"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL

OUR readers will no doubt remember, for it was quoted in the Journal as recently as last November, the late Professor Haldane's definition of the death of the body as "The mysterious dissolution of the association together of the infinitely complex group of normals which constitute the life—the φυσις—of an organism." "The association together of the infinitely complex group of normals which constitute the life—the φυσις—of an organism" receives further exemplification in the two remarkable articles in the present number, one by Professor Burn and the other by Professor Paton.

It is not many years ago that the importance of the concentration of electrolytes in the blood began to be generally appreciated by clinicians. One remembers the impact of Marriott's (1947) original papers and how they focused attention on the salt content of urine in patients after operation. Since that time the importance of the potassium ion has become apparent. Now the part played by the hormones of the adrenal cortex in regulating sodium and potassium excretion has demanded attention and influenced our approach to the body's reaction to trauma. In his paper Professor Burn reviews this subject and also shows how tumours of the adrenal cortex may result in secretion of excessive amounts of aldosterone, thus diminishing sodium excretion and increasing that of potassium, which alteration in electrolyte distribution to some extent disturbs the buffering activity of the blood. In considering the medullary secretion of adrenaline and noradrenaline he makes the interesting suggestion that vasopressin might be useful in cases where it is difficult to interrupt an adrenaline drip because of the depression of transmission of impulses from preganglionic to postganglionic fibres which adrenaline produces. Vasopressin has no such action.

Professor Paton finds that the story of the neuromuscular block has become more complicated of late, and it is hoped that his exposition will clarify the position for our readers. Here again he stresses the importance of the ionic environment as a condition of the phenomena observed.

A perusal of these papers would seem to suggest the desirability of all our leaders, politicians, trade unionists, and others taking a course in advanced physiology before they assume office. A knowledge of how the health of the body depends on "the association together of the infinitely complex group of normals" might do much to teach them how the health of the body politic could be similarly ensured.

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A NEW METHOD OF SPIROMETRY APPLICABLE TO ROUTINE ANAESTHESIA

BY

J. F. NUNN

Department of Surgery, University of Birmingham

McKESSON stressed the importance of measuring minute volume during anaesthesia as long ago as 1922. He found, using a graduated rebreather with a demand apparatus (1922), that there were very great variations in ventilation, including considerable under-ventilation, during ether anaesthesia (1928). There was little further work involving measurement of respiratory volumes until Ament, Suskind, and Rahn (1949) described the measurement of minute volume by expiring through unidirectional valves into a gasmeter, during thiopentone anaesthesia. Ridley and Faulconer (1952) and later Zinberg and Jensen (1954) have described the use of gasmeters in a modified circle system. Gasmeters have a high degree of accuracy in measuring flow, but leakage at the unidirectional valves, as the author has confirmed, can cause considerable errors.

The first attempt to measure respiratory volumes in the familiar partial rebreathing system was made by Benson (1951), who described a bellows type of spirometer which could be used with a semiclosed system as well as in a closed system with basal flow rates. With the semiclosed system the recorded tidal volume was usually within 10 per cent of the true value. However, the error depended greatly on the flow rate of fresh gases. The method was used by Reve, Nanson and Rundle (1951) and in a modified form by Eastwood and Harbord (1955), who used no gaseous anaesthetic agent and basal oxygen flows.

Lund, Andersen and Erikson (1956) recorded the ventilation with a Water's to-and-fro system of which the bag was enclosed in a box in communication with a spirometer. This appears to offer no advantage over the simple replacement of the bag by a spirometer. The author used this latter technique some years ago and found that varying the rate of fresh gas supply and variable venting from the relief valve caused very great inaccuracy and the method was of no real value.

The only method of avoiding this source of error is the use of basal flows in a completely closed system. However, there is no certain way of detecting dangerous changes in the inspired gas tensions which may occur, and for this reason the semiclosed system with a high gas flow is preferable. Woolmer (1956) has recently described the use of a Pauling meter to monitor the oxygen tension in the inspiratory limb of the closed circuit. This has removed the greatest objection to the system, but at present the expense and difficulty in obtaining a Pauling meter

precludes the general adoption of oxygen monitoring. Basal flow of gases is seldom used in clinical anaesthesia, and the respiratory volumes under this form of anaesthesia will not necessarily correspond to those under other methods.

A different approach being investigated by several workers is the measurement of the flow rate of the gases entering and leaving the patient. This may be achieved with the pneumotachygraph introduced by Lilley (1950) which measured the pressure differential across a Monel metal screen in the airway. However, it is necessary to convert flow rates to volumes, which requires electrical or planimetric integration, neither of which is a simple procedure. There are considerable difficulties in the application of the pneumotachygraph to anaesthesia as the apparatus has a large dead space. In addition, the variable viscosity of the different gases passing the screen would introduce error.

Maloney, Derrick, Whittenberger and Isaacs (1952) introduced a venturi system in which the pressure differential produced was the same for gas flow in either direction. By damping it was possible to obliterate the fluctuations caused by single breaths and thereby register the mean inspiratory and expiratory gas flow. In normal circumstances this would be proportional to minute volume. It was therefore possible to calibrate the differential pressure gauge to record the minute volume. This apparently simple device may be of great value in the operating theatre, but, surprisingly, there appear to be no further reports of its use in anaesthesia.

A respiratory anemometer of wind vane type has been described by Wright (1955) which measures volume directly, and with its small bulk it would seem to be suitable for inclusion in anaesthetic circuits. However, it is likely that condensation may cause inaccuracies.

The author wished to develop a method of measuring ventilation during the administration of an anaesthetic with the circuits in common use and in which the accuracy would not be affected by the flow rate of fresh gases. Previous methods have either altered the method of administration of the anaesthetic or sacrificed accuracy. Thus there is little accurate knowledge of the ventilation under the conditions of routine anaesthesia, though the subject is of the greatest importance in view of the possibility of considerable under-ventilation and hypercarbia during spontaneous breathing in the anaesthetized patient.

Carbon dioxide retention in the anaesthetized patient may occur for three reasons. First, there may be reduced sensitivity of the respiratory centre to carbon dioxide. Secondly, relaxants cause a peripheral impairment of the respiratory mechanism, and thirdly there may be re-inhalation of carbon dioxide. It was considered that as a prelude to investigations on gaseous acidosis in anaesthesia it was necessary to design a spirometer which would allow the measurement of respiratory volumes and the response of the breathing to the various gas mixtures inhaled during the normal course of clinical anaesthesia.

THE PRINCIPLE OF CONTINUOUS FLOW SPIROMETRY

In any anaesthetic system employing a reservoir bag and a relief valve the inhala-

tion is derived partly from the volume changes in the bag and partly from the fresh gases supplied during inspiration from the anaesthetic machine. Exhalation is partly towards the bag and partly to atmosphere through the valve. Thus any system of measuring ventilation from movements of the reservoir bag alone is at best an approximation.

The change in volume of the bag may be measured by enclosing the bag in a rigid box connected to a spirometer as described by Donald and Christie (1949). The gas vented by the relief valve may be ducted into the box (outside the bag) so that it will be summated with the volume changes brought about in the box-spirometer system by the movements of the bag. There remains the steady flow of gases from the anaesthetic machine, and this may be accounted for by aspirating from the box an equivalent volume at a steady rate. Under these conditions it will be seen that the volume changes in the box-spirometer system will represent the tidal excursion of the patient.

The application of this principle to various anaesthetic systems is shown in figure 1. All circuits employing a reservoir bag and relief valve are basically similar so far as spirometry is concerned. T-piece anaesthesia presents a difference in that there is no reservoir bag and the tidal volume is measured as the difference between the volumes passing the two limbs of the T-tube leading to and from the patient.

Before starting to record, the rate of

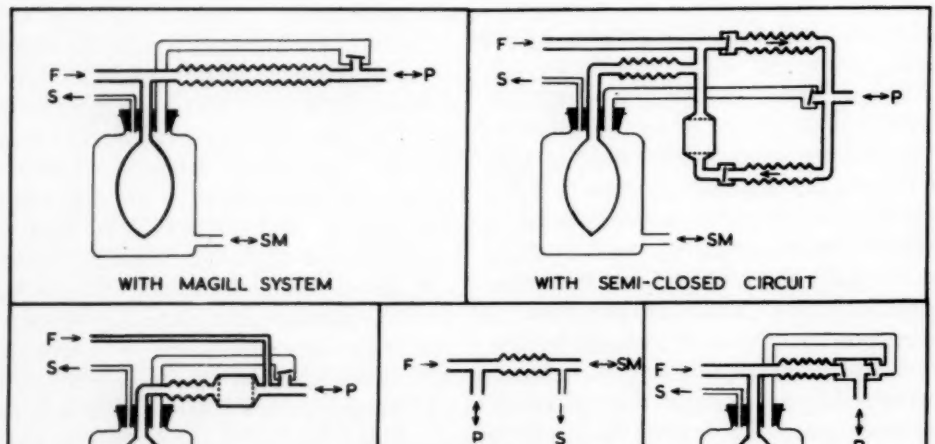

FIG. 1
The application of continuous flow spirometry to various anaesthetic systems.

suction is adjusted to equal the fresh gas flow rate. This may be done by occluding the connection which will lead to the patient and then altering the rate of aspiration until the spirometer remains steady. During respiration, however, a number of factors may cause the tracing to rise or fall. Benson (1951) found that the volume of the functional residual air tended to vary during anaesthesia. With changing ventilation the ratio of carbon dioxide eliminated to oxygen taken up fluctuates markedly. Thus during a period of hypoventilation the respiratory quotient falls, causing the tracing to rise as the spirometer falls. Anaesthetic gases are taken up and eliminated in very large quantities, and, furthermore, there is the addition of water vapour to expired gas. These factors are subject to frequent change and it is necessary to alter the rate of suction from time to time to keep the tracing level. With the large number of factors affecting the gradient of the tracing the utmost reserve is needed in pronouncing on a change as being due to any particular cause.

With certain types of relief valve which have a high resistance an excessive pressure is created in the bag and connecting tubing at the end of expiration. A correction must be applied to the tidal volume as this compressed gas records as though it were at atmospheric pressure. The correction factor is a function of the pressure attained and the volume of gas in the system under this pressure. It may be minimized by the use of a valve of low opening tension and low viscous resistance. With the Heidbrink type of valve on the Magill circuit the correction factor is of the order of 20 millimetres.

It is not possible at present to see how this method of spirometry could be applied to controlled ventilation. It is essential that the reservoir bag should be enclosed and that there should be a minimal pressure difference between the inside and the outside of the bag.

THE SPIROMETER

The diameter of the bell was reduced to half that of the 5-litre Benedict Roth spirometer. This ensured an adequate excursion for recording the small tidal volumes of the anaesthetized subject, but there was a tendency to overshoot, there being a fourfold increase in linear velocity which imparted a high kinetic energy to the moving bell.

Bernstein and Mendel (1951) and Bernstein, D'Silva and Mendel (1952) investigated the problems of inertia and resonance in connection with estimating maximum breathing capacity. They suggested keeping the inertia of the moving parts to a minimum by reduction in weight and by substituting two small pulleys in place of one large one in the suspension. In addition the design of the tank was altered to raise the resonant frequency of the system as much as possible.

In the construction of the spirometer for anaesthetic use it was possible to keep the weight of the moving parts very low, and the resonant frequency was 96 with the bell immersed to a depth of 5 centimetres. Nevertheless, in view of the high linear velocity, it was not surprising to find that there was considerable overswing which was roughly proportional to the frequency.

The response of the spirometer to changing frequency was investigated with

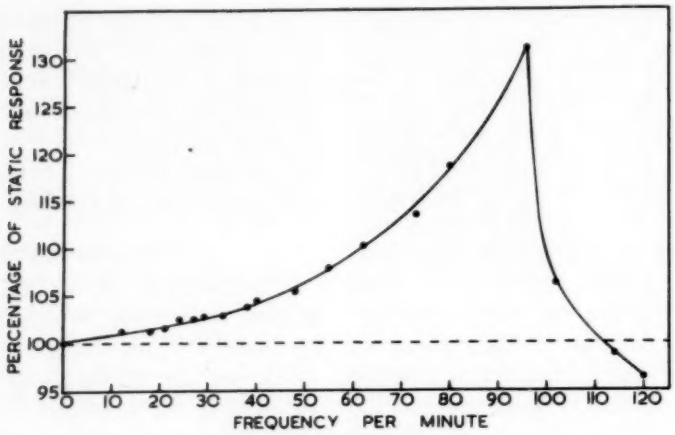

FIG. 2
The frequency response of the spirometer alone at a stroke volume of 281 ml.

a four-cylinder reciprocating pump of variable rate and stroke volume. The results throughout the range of the pump's speed are shown in figure 2. Figure 3 shows in greater detail the response up to a frequency of 40 per minute for five different stroke volumes. Over this range the following equation is applicable with a maximum error of 0.7 per cent.

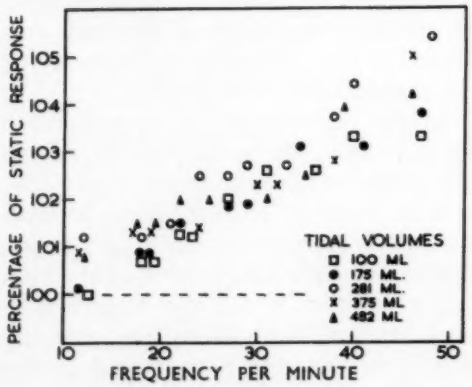

FIG. 3
The frequency response of the spirometer alone at various stroke volumes over the clinical range of frequencies.

$$\text{True response} = \frac{\text{Observed response}}{1 + 0.0013\ (f-6)}$$

where f represents the frequency.

In an anaesthetic system containing a rubber reservoir bag the frequency response was entirely different (figures 4 and 5). Both the Magill and the valvular no-breathing systems (as shown in figure 1) were investigated, and in each case the general form of the curves was similar. It did not appear to be modified by varying flow rate or tidal volume. Up to a frequency of 35 per minute the response

TABLE I
Specifications of the Spirometer

Capacity of bell	2 litres
Diameter of bell (internal)	9.2 cm
Length of bell	30 cm
Weight of bell	89.5 grams
Thickness of bell	0.314 mm
Material of bell	Anodized aluminium
Diameter of core (external)	7.9 cm
Distance from core to sides of tank	6.8 cm
Weight of counterweight including pen writer	75.5 grams
Suspension	thin cord
Pulleys, two in number, 1½" diameter, aluminium mounted on ball races.	

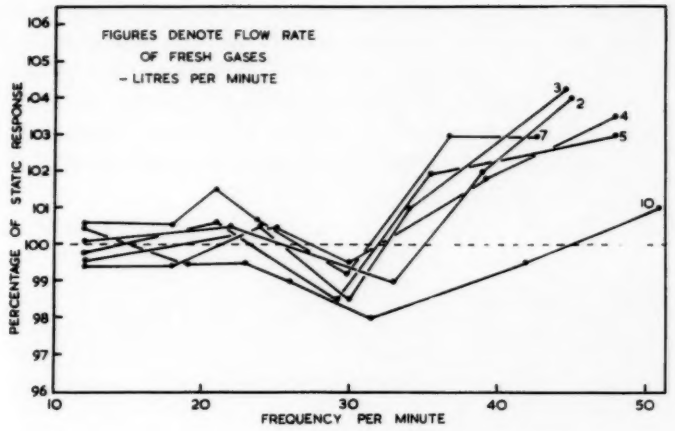

FIG. 4

The frequency response of the spirometer in conjunction with the Magill semiclosed system at a stroke volume of 417 ml. The pressure correction factor has been applied.

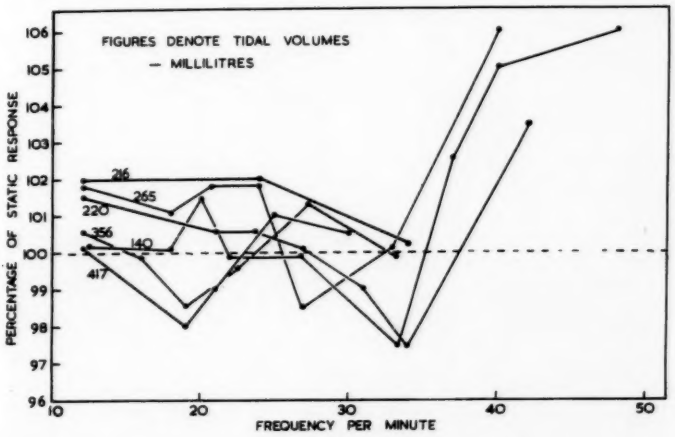

FIG. 5

The frequency response of the spirometer in conjunction with the valvular no-rebreathing system with a fresh gas flow rate of 10 litres per minute.

was within 2 per cent of the static response and in this type of work such an error may be accepted without correction. Few patients under general anaesthesia have a higher respiratory rate than 35 and in that event a correction factor could be determined from the graph.

The spirometer was calibrated by displacement of gas by water and found to be linear within 0.3 per cent. The sensi-

tivity was 67.0 ml per cm of linear excursion of the bell. The resistance to inflation of box-bag and spirometer combined, at a flow rate of 10 litres per minute, did not exceed 1 mm water over the range used.

The general arrangement of the apparatus is shown in the photograph (figure 6) where it will be seen that the trolley carries flow meters and is, in fact, a self-contained anaesthetic apparatus. It was found possible to comply with the recommendations for the prevention of explosions. The use of plastic was avoided and all switches were of the mercury spark-proof type.

The suction is provided by a small

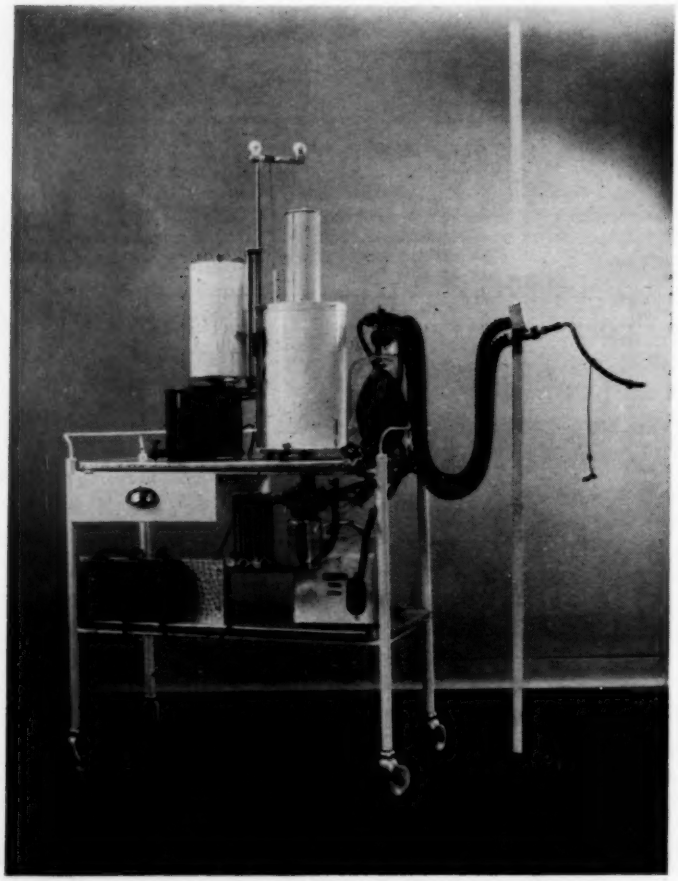

FIG. 6

The continuous flow spirometer mounted on trolley to record respiration while using the Magill semiclosed system. The boxed relief valve may be seen next to the endotracheal mount and the fine adjustment valve for aspiration is on the right of the upper shelf.

diaphragm pump (lower shelf) with a capacity of 20 litres per minute and a potential vacuum of 500 mm Hg. The rate of aspiration of gas is controlled by a fine adjustment valve which may be seen at the top righthand corner of the trolley in the photograph.

The reservoir bag is contained in a 5-litre aspirator jar with a wide neck which admits the various connections except for the tubing to the spirometer which leaves the jar separately at the base.

The tracing is made on a continuous roll of paper which permits the making of tracings of any duration. There is a time marker which forms a convenient base line to which the expiratory level of the tracing may be adjusted.

Figures 7 and 8 show the type of tracing which may be obtained. Figure 7 shows the use of pethidine to restore the depth of anaesthesia following the undesired return of reflexes from the respiratory tract. It demonstrates the variations in the level of the functional residual air which may be encountered especially when the level of anaesthesia has become too light. Figure 8 records the respiratory response to suxamethonium. After the onset of apnoea the tracing is interrupted to permit controlled respiration. Thereafter the respiration rapidly returns to its original tidal volume. Figure 9 shows the graphical presentation of data obtained with the spirometer. The respiratory rate, tidal volume and minute volume are shown with simultaneous records of end tidal carbon dioxide tension, blood pressure and pulse rate.

SUMMARY

(1) A new method of spirometry has been described which is applicable to most anaesthetic systems in routine use.

(2) The accuracy is not significantly impaired by alterations in the rate of supply of fresh gases.

(3) The frequency response has been determined for the spirometer itself, and

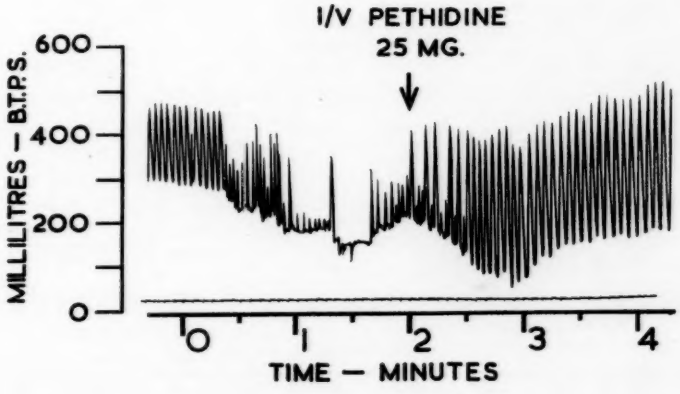

FIG. 7

A sample tracing showing the effect of pethidine in restoring the depth of anaesthesia.

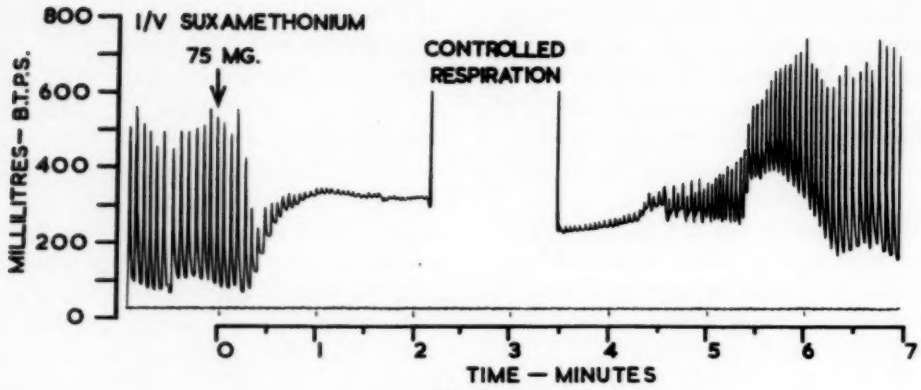

FIG. 8
A sample tracing showing the effect of suxamethonium.

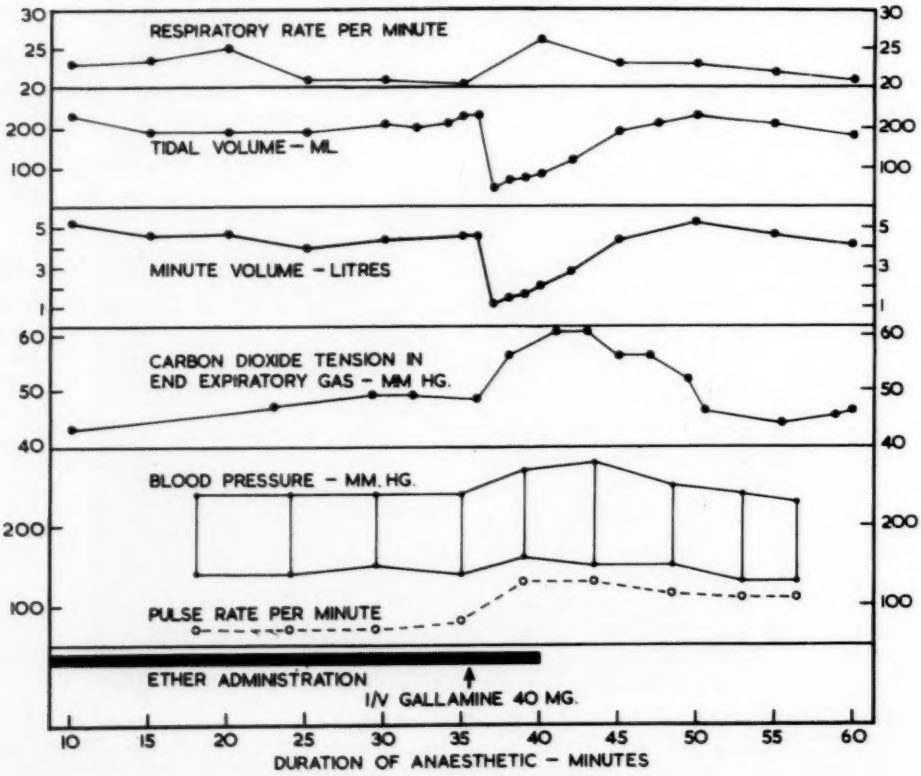
RESPIRATORY RATE PER MINUTE
TIDAL VOLUME – ML.
MINUTE VOLUME – LITRES
CARBON DIOXIDE TENSION IN
END EXPIRATORY GAS – MM. HG.
BLOOD PRESSURE – MM. HG.
PULSE RATE PER MINUTE
ETHER ADMINISTRATION
I/V GALLAMINE 40 MG.
DURATION OF ANAESTHETIC – MINUTES

FIG. 9
Graphical presentation of data obtained with the continuous flow spirometer during appendicectomy in a hypertensive patient.

in conjunction with the Magill attachment and the valvular no-rebreathing system.

(4) In normal anaesthetic use the accuracy is within 2 per cent up to a frequency of 35 per minute.

(5) A few records of results obtained with the spirometer are given.

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I wish to express my appreciation to Mr. H. A. Crisp for his excellent workmanship in the construction of the spirometer.

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CORRESPONDENCE

CARDIAC ARREST FOLLOWING THE ADMINISTRATION OF NEOSTIGMINE

Sir,—Dr. Lawson's description of a case of cardiac arrest following neostigmine injected simultaneously with atropine (*Brit. J. Anaesth.* (1956), **28**, 336) raises several interesting points.

Firstly, is 1/100 grain (0.6 mg) of atropine sufficient to neutralize the vagal effect of 2.5 mg of neostigmine? Some authorities (Lee) recommend a dose of 1/50 grain (1.2 mg). This is supported by the fact that the pulse is usually slower after the injection of atropine 1/100 grain (0.6 mg) and neostigmine 2.5 mg (whether separate or combined) than it was before the injection of the drugs.

The injection of 1/50 grain (1.2 mg) of atropine may, however, give rise to a very rapid tachycardia which is undesirable. One solution to the problem, which I have used, is to inject 1/100 grain (0.6 mg) of atropine and then to follow this three or four minutes later with a mixture of a further 1/100 grain (0.6 mg) of atropine plus the 2.5 mg of neostigmine. With this method it will be found that the pulse is approximately the same after as it was before the administration of the drugs.

In the second place one feels that some attention should be paid to the actual pulse rate immediately before the injection of the drugs. It is, I think, significant that the pulse rate in the case described by Dr. Lawson was slow at the time of injection. If the pulse is slow the vagal tone is likely to be high and a full total dose of 1/50 grain (1.2 mg) atropine will be required. If, however, the pulse is rapid the vagal tone is probably minimal, less atropine will be required, and the two drugs can be injected together with comparative safety. This hypothesis would hold whether or not it is true that atropine has an initial stimulant action on the vagus.

TOM B. BOULTON
Ann Arbor, Michigan, U.S.A.

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ANAESTHESIA FOR CARDIOVASCULAR AND NEUROSURGICAL RADIOLOGICAL INVESTIGATIONS

BY

D. DUNCALF AND P. W. THOMPSON

Department of Anaesthetics, Welsh National School of Medicine, Cardiff

INTRODUCTION

ANAESTHESIA enables the radiologist not only to carry out procedures which would otherwise be impracticable but to do so with considerable safety on patients who would ordinarily be regarded as bad anaesthetic risks. An appreciation by the anaesthetist of the requirements necessary for good radiological work is dependent on knowing something of the techniques themselves. We therefore outline the aims and methods of the radiological procedures, in addition to giving our personal experience of the anaesthetic problems.

Indications for general anaesthesia. General anaesthesia is necessary when the patient is either unco-operative or very apprehensive, when the procedure is uncomfortable or painful, or to prevent movement of the part concerned.

The explosion risk. Ideally the anaesthetic should be non-explosive. It may be, however, that the alternative to an explosive anaesthetic is considered to be more hazardous than the risk of explosion (Macintosh and Mushin, 1954).

Maintenance of a clear airway. This is particularly important in a darkened room where cyanosis may be missed and the flowmeters may not be clearly seen.

Preparation of patient and apparatus. In the X-ray department anaesthesia may be an occasional event and patients are often from wards unaccustomed to preparation for anaesthesia. For these reasons the anaesthetist himself should check such things as when the patient last took food or drink and the presence or absence of dentures. It is all too easy to assume that the facilities of a busy operating theatre will be automatically present elsewhere. A check of all the possible needs before starting may help to avert a disaster.

Dangers of radiation. If attendance in the X-ray department becomes a regular feature in the work of an anaesthetist he must take precautions against the effects of radiation upon himself (Inglis, 1954).

The radiological investigations to be considered here fall into two groups.

Cardiac investigations.
- Cardiac catheterization.
- Angiocardiography.

Neurosurgical investigations.
- Cerebral angiography.
- Encephalography.
- Ventriculography.

CARDIAC INVESTIGATIONS

Cardiac catheterization was first carried out by Forsmann in Germany on himself in 1929. It was he also who first injected dye into the catheter.

Cardiac catheterization involves the passage of a catheter via one of the peripheral veins (usually in the arm) into the heart and great vessels. The advance of the catheter is controlled by fluoroscopy. By measuring pressures and blood gas concentrations in the various chambers of the heart and great vessels, cardiovascular lesions may be diagnosed. An increased blood oxygen concentration in a blood sample taken from the right heart, for example, indicates the presence of a left-to-right shunt. If dye (e.g. Evans Blue) is injected and its blood concentration measured at intervals, these values plotted against time produce "a concentration curve". Certain patterns are characteristic for left-to-right and right-to-left shunts.

Angiocardiography consists of rapidly injecting diodone through a wide bore cannula tied into an antecubital vein, or through a polythene tube passed up this vein into the subclavian vein or superior vena cava. Immediately after the injection a series of X-ray pictures of the chest is taken in rapid succession.

These two investigations are really complementary and occasionally both are performed on the same patient. By these means suitable cases for surgery can be selected and the results of such surgery may be more exactly assessed.

Usually general anaesthesia will be needed for cardiac catheterization and angiocardiography for children below the age of 12, to avoid crying and struggling.

These children are often cyanosed. Frequently in congenital heart disease the patient is undersized and recurrent respiratory infections are common. Congenital defects are often multiple; for example, the authors have anaesthetized a child 8 weeks old and weighing $6\frac{1}{2}$ lb, (3.0 kg), who not only had had cyanotic attacks since birth due to a presumed pulmonary stenosis but had a number of other defects, including malformation of the ribs, hemicervical vertebrae, and a malplaced anus.

According to Cournand et al. (1953), the absolute contra-indications to cardiac catheterization are ventricular tachycardia, recent myocardial infarction and subacute bacterial endocarditis.

Cardiac Catheterization

The aims are to put the child asleep with as little disturbance as possible, to maintain light anaesthesia for perhaps an hour or so, to prevent fluctuations of blood pressure and heart rate, and, when blood gas analysis is to be made, to do this in such a manner as not to disturb the normal blood gases.

Anaesthesia.

This consists of rectal bromethol (Avertin) together with additional agents by inhalation or intravenous injection when required. Rectal bromethol in children has been used successfully at Sully Hospital for radiological procedures for several years (Mushin and Lake, 1951).

The children have nothing by mouth for 4 hours before the investigation. Atropine (0.3–0.65 mg) depending upon age and weight is given one hour before the catheterization. The bromethol is given on a dosage basis of 125 mg/kg body weight for the average case. No preliminary enema is required and no undue pressure should be used to instill the solution. Twenty minutes is taken over the

administration, after which the buttocks are strapped together. Generally, the child will be asleep at the end of this time and the maximum effect develops 30 minutes later.

Bromethol depresses the respiratory centre and produces a moderate fall in blood pressure. Often the colour of cyanosed cases improves when bromethol has been used because metabolism and tissue oxygen requirements are reduced. It is essential that the patient should be supervised by a competent nurse until handed over to the anaesthetist. She must be able to deal efficiently with respiratory obstruction which can easily occur as the patient lapses into unconsciousness.

On arrival at the X-ray room the child will be asleep but should react to painful stimuli. The intravenous catheter is introduced after infiltration with 0.5 per cent lignocaine.

The needle prick is the strongest stimulus during the whole procedure. The temptation to try to abolish completely the reaction which follows, by the use of supplementary agents, should be avoided, or the resulting anaesthesia will be deeper than necessary and recovery time unduly prolonged. An assistant should keep the injection site stationary during the infiltration since only light anaesthesia is produced.

Originally only nitrous oxide, oxygen and trichlorethylene were used when additional anaesthesia was needed. This was administered via the face mask of a Boyle's apparatus. More recently we have preferred to use pethidine as the sole supplement because of certain disadvantages of the first method. Trichlorethylene has the reputation of frequently producing cardiac arrythmias although in our experience the electrocardiogram remains normal, any arrythmias only being seen when the catheter enters the heart. A face mask is not a very satisfactory way of administering an anaesthetic to small infants. The dead space of the mask together with the natural dead space is relatively large compared with the patient's tidal volume, and the resistance of valves and tubes may be heavy for the child and carbon dioxide retention, a cause of cardiac arrythmias, may occur. Also trichlorethylene tachypnoea is particularly undesirable in these cases.

The pethidine is suitably diluted and injected through a diaphragm needle or the intravenous catheter once it is in place. Each dose does not exceed 0.5 mg/stone (6.4 kg) and usually 3–4 doses are needed. A wait of at least 5 minutes is made before giving a further dose of pethidine.

Some tone persists in the tongue and jaw muscles and a pharyngeal airway is rarely needed. With very cyanosed patients who have been in an oxygen tent it is desirable to continue the administration of oxygen.

Excessive exposure of the patient to X-rays which may depress the function of the bone marrow should be avoided. This is a very real danger, particularly in these cases as the haemopoetic system may be hyperactive and especially vulnerable to X-rays.

Generally the patients who are anaesthetized in this way move about 20 minutes after the cessation of the administration and are almost "round" before reaching the ward. They do not complain and usually ask for something to eat as soon as they recover consciousness fully.

Larger children are more restless post-operatively than the smaller ones, and some may even require mild restraint. Vomiting is uncommon.

Complications associated with the cardiac catheterization.

Rhythm disturbances are the most important of these. Premature ventricular contractions are frequent when the catheter is inside the heart, usually when the tip is being passed through the tricuspid valve or lies against the ventricular septum in the region of the outflow tract. Ventricular tachycardia is fairly rare and may precede ventricular fibrillation. Auricular tachycardia, premature auricular beats, auricular fibrillation, and bizarre electrocardiographic changes are occasionally observed and usually transient. Conduction disturbances are fairly common.

Changing the position of the catheter almost always results in the disappearance of the arrythmia. Occasionally auricular arrythmias have persisted several hours after the completion of the procedure, subsiding spontaneously or with treatment. Rare complications include bronchospasm, and trauma to the heart itself. The only case in our experience causing alarm was a small child having cardiac catheterization who developed ventricular tachycardia and collapsed. This rhythm was reversed by procaine amide. In another case a nodal rhythm developed which persisted for ¼ hour after the catheter was withdrawn.

Angiocardiography

Anaesthesia.

This is a much shorter procedure than cardiac catheterization. We use the same means to produce anaesthesia. In addition suxamethonium, 5 mg/stone (6.4 kg) is injected intravenously just before the dye. The lungs are rhythmically inflated with oxygen until adequate spontaneous respirations return.

A short period of apnoea is permitted while the X-rays are taken. By using suxamethonium in this way convulsive coughing which otherwise may occur 2–10 seconds after the injection of dye is prevented (Carnegie, 1951).

The administration of pure oxygen prior to the injection of diodone seems desirable as bronchospasm is a particularly dangerous complication following the injection.

Complications associated with the angiocardiography.

Moderate to severe sinus tachycardia appears within the first minute following the injection of diodone and usually persists for 5–10 minutes (Adelman et al., 1952). Electrocardiographic abnormalities include premature ventricular contractions, flattening and inversion of the T-waves and prolongation of the Q-T interval. Some electrocardiographic changes suggest myocardial anoxia, possibly due to constriction of the coronary arteries. The blood pressure always falls within 1–2 minutes of the injection of the diodone, this fall being considerable in some cases; it is usually about 5–8 minutes before it starts to rise again.

Treatment of complications of cardiac catheterization and angiocardiography.

Cardiac catheterization should be terminated if there is a significant increase in heart rate or evidence of vagal stimulation and if there is persistence of in-

duced premature ventricular contractions or right bundle branch block. We consider procaine and/or quinidine should not be used prophylactically to reduce the incidence of cardiac arrythmias particularly if angiocardiography is being performed, as diodone must itself be regarded as a powerful depressant of heart muscle (Adelman et al., 1952).

Efficient suction should be at hand to deal with excessive pulmonary secretions. Severe hypotension should be treated by placing the patient in the Trendelenburg position and administering oxygen. Bradycardia is treated with atropine. A vasopressor drug and atropine must always be at hand for use in such emergencies.

The patient is carefully supervised after an angiocardiography for at least 15 minutes, as it is during this period that death is most likely to take place (Dotter and Jackson, 1950).

NEUROSURGICAL RADIOLOGICAL INVESTIGATIONS

Until recently very little had been written on the problems of anaesthesia for these investigations (Geddes, 1952; Coles, 1953).

Ventriculography and Encephalography

Deformities of the ventricles by intracranial lesions may be demonstrated radiologically by filling the ventricles with air. In ventriculography this is accomplished by the direct injection of air into the ventricles. The operative technique is still Dandy's (1918) original one of "a burr-hole and ventricular tap", and is usually performed under local analgesia. In lumbar encephalography the subarachnoid space is also outlined. A lumbar puncture is performed with the patient in the sitting position and air is injected into the subarachnoid space after removing c.s.f. The injection of air commonly causes severe headache, but the inhalation of oxygen postoperatively often relieves this (Macintosh and Mushin, 1946). Immediate collapse of the patient may occur. Some workers therefore advise general anaesthesia for all these cases. Even under general anaesthesia, some movement of the patient, an increase in limb rigidity, or an altered pattern of respiration, may occur at this point.

The dangers of encephalography and ventriculography are:

(1) A rise in intracranial pressure.
(2) Vomiting; this may occur very suddenly during the injection.
(3) Coma.
(4) Haemorrhage.

If the intracranial pressure is already high before the investigation is started, facilities for the performance of emergency craniotomy as a lifesaving measure must be available.

Cerebral Angiography

The outlining of a blood vessel by radiological contrast media is applied to many vessels of the body. Carotid and vertebral angiograms are employed in the investigation of intracranial lesions. The contrast medium now used is diodone.

A carotid angiogram demonstrates most of the vessels above the tentorium, and if the injection is made into the common carotid artery the dural, scalp and neck vessels are shown as well. Vertebral angiography outlines the vessels of the posterior fossa and the posterior cerebral arteries. Local analgesia for angiography

consists of an infiltration of the tissues of the neck through which the injecting needle will be passed.

The dangers of angiography are:

Local:

(1) Cerebral embolism, with either air or blood clots.
(2) Haematoma of the neck. This may rarely cause respiratory obstruction.
(3) Sepsis.

General:

(1) Renal failure in nephritis. The investigation is therefore contra-indicated in cases of renal disease, advanced cardiac disease and hypertension.
(2) Iodine reaction in sensitive individuals.
(3) Convulsions. These are rare.
(4) Raised intracranial pressure. If there was an already high pressure, immediate operation may be essential.

General Anaesthesia for Neurological Investigations

There are several points in technique which merit special consideration.

Intubation.

It is desirable to intubate all these cases to ensure a clear airway. Special care must be taken with children, so that teeth are not dislodged with the laryngoscope and that the tube does not enter one of the bronchi. An endotracheal tube in a child may impact at the cricoid ring, the narrowest diameter of the larynx. Force in this event may cause severe damage. In the child the larynx is angulated forwards and the end of the tube frequently presses against the anterior wall. Intubation may be facilitated by a slight backward pressure on the "Adam's apple". A very light pack may be put around the tube in the pharynx to ensure that the mixture inhaled by the patient from the anaesthetic machine is not grossly diluted with air inhaled around the tube.

There is considerable movement of the head during these investigations which causes the tube to rub against the vocal cords. The oedema of the larynx which follows will probably not cause any obvious trouble in an adult, but in a child may produce serious respiratory obstruction. The child must be carefully watched at the time of extubation, and for some days afterwards, for any signs of respiratory embarrassment.

Thin rubber endotracheal tubes are liable to kink when the neck is flexed. Armoured tubes are not free from danger. A spiral of the strengthening wire may be bared after boiling has softened the covering, and the wire may even uncoil itself. The rubber cover may split into layers with obstruction of the lumen of the tube (Burns, 1956). For these reasons we use a Portex tube in every case. We have, however, found that even Portex tubes may kink quite easily. The presence of such an obstruction may pass unnoticed unless it is complete. It will, however, be clearly seen on the X-ray films.

Alterations in the position of the patient may involve changes in the fixation of the anaesthetic breathing tube around the X-ray apparatus. Various endotracheal connections have been devised, to make this easy. One example is illustrated (fig. 1). The swivel connection allows of

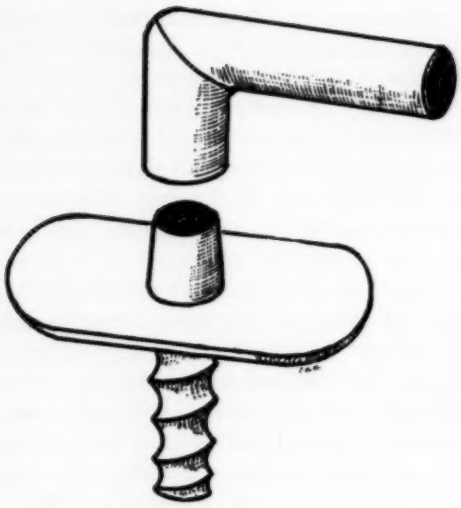

FIG. 1
Swivel endotracheal tube connector.

very easy separation of the connecting tube in order to rearrange the corrugated tubing.

Vomiting.

Some patients may vomit when diodone is injected. An empty stomach is a prerequisite for any patient about to have a general anaesthetic, but the greater possibility of vomiting in these cases must not be overlooked, and means to treat it must be ready.

Carbon dioxide accumulation.

In these cases rebreathing must be kept to a minimum. This is achieved when the semi-open circuit is used, by such means as keeping the flow rate of gases above the respiratory minute volume (Mapleson, 1954), using an Ayre's T-piece, or inserting a safety pin under the leaf of the expiratory valve to reduce its resistance to an absolute minimum. Any accumulation of carbon dioxide in the patient's blood will lead to an undesirable rise in intracranial pressure.

Absence of coughing.

The effects of spasms of coughing on the intracranial pressure are well known. Any movement of the neck during an angiogram can also easily displace the needle from the artery with the possibility of extravascular injection of diodone. In addition, the stimulus of the injection may make the patient cough, if lightly anaesthetized. This too may result in extravascular injection.

Immobility.

Any movement of the patient must be avoided. The anaesthetist may give a minute dose of thiopentone just before the injection of air or diodone to make sure that the patient does not move at this critical moment.

Artefacts.

The anaesthetist should see that there are no creases in any adhesive strapping which he may have used to secure his endotracheal tube. Such creases may show up as deceptive faint lines on the film.

Venous engorgement.

Venous engorgement of the neck facilitates the accidental puncture of a vein by the injection needle and the formation of a haematoma. This may be sufficiently extensive to interfere with the palpation of the carotid vessels and the operation may have to be postponed until the haematoma has resolved. To this end anoxic episodes must be avoided, and constrictions around the neck such as the top drawstrings of a child's nightdress must be removed before anaesthesia is induced.

Cardiovascular disturbances.

The variations of posture occurring during these techniques may cause cardiovascular disturbances. The commonest of these is a fall in blood pressure when the patient is moved from the horizontal to the sitting position. The resulting decrease in the cerebral circulation may have particularly deleterious effects on these patients.

The injection of diodone may cause hypotension due to a generalized vasodilatation and this has on occasion been gross enough to precipitate hemiplegia (Geddes, 1952). In other cases hypotension caused transient attacks of blindness. Hemiplegia has also followed vasospasm in the vessels of the brain. In these cases stellate ganglion block has appeared to give some improvement. However, these complications are fortunately rare. Any spasm which does occur is probably due to some of the injection being extravascular where it irritates the vessel.

Anaesthesia.

Premedication consists of atropine and, if the patient is not comatose or has no raised intracranial tension, an opiate. In the case of younger children it is probably better to use atropine only. Rectal thiopentone, 1 g/50 lb (23.5 kg) body weight, may be used in selected cases.

Induction of anaesthesia is usually with thiopentone sodium. If no vein is apparent, the smaller children are given ethyl chloride and ether, preferably outside the X-ray room. When intravenous thiopentone is used it is followed by a muscle relaxant. We favour gallamine. If a shorter acting relaxant such as suxamethonium is used its effects wear off quickly and a lightly anaesthetized patient may start to cough violently on the endotracheal tube soon after it is in place. Gallamine, by virtue of its vagolytic activity, may assist in the prevention of the cardiovascular effects which have followed the insertion of the needle into the carotid sinus.

The cords are sprayed with a weak cocaine solution which allows even easier intubation and makes for smoother anaesthesia. A few puffs of the spray over the endotracheal tube after it has been smeared with K.Y. jelly may prove helpful.

Anaesthesia is maintained with nitrous oxide, oxygen and trichlorethylene. Pethidine is used for supplementation if indicated.

SUMMARY

(1) A brief outline of the aims, methods and special dangers of the radiological techniques in common use for the investigation of cardiac and neurosurgical lesions is given.

(2) General anaesthesia for these cases is discussed, special reference being made to points in anaesthetic technique which make for efficiency and safety.

ACKNOWLEDGMENT

We would like to record our thanks to Professor W. W. Mushin for his constant encouragement and advice in the preparation of this paper. Thanks are also due to Mr. E. K. Hillard, Senior Technician, for preparing the diagram.

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BOOK REVIEW

Techniques and Procedures of Anaesthesia (2nd edition). By John Adriani, M.D.. Professor of Surgery and Pharmocology, Louisiana State University. Published in this country by Blackwells of Oxford. Price 66s.

Any teacher of anaesthetics would save himself much time and trouble if he bought this book. He would find the basis of a long course of lectures on anaesthetic techniques already arranged for him. The reasons for and against the various procedures and comments thereon are clearly set out. He would be able to vary the monotony, the inevitable monotony, of a book of this sort and vivify his lectures by illustrations from his own experience; but the basis for them has already been done for him. A more commonsense and saner account it would be difficult to find.

There are so many differing techniques that it is quite impossible for one anaesthetist to have had a large experience in all of them; this fact will necessarily influence his choice, and he may find that the order set out in table 2 is not the order he himself would choose. In his introduction Dr. Adriani mentions a number of factors which influence the choice of the anaesthetic, amongst them the skill and dexterity of the surgeon. Surely the skill and dexterity of the anaesthetist is another, but he doesn't mention it. Are we to gather that American anaesthetists are "circled through all experiences to ensure perfect freedom"?

There are 17 tables and 194 illustrations, together with a useful appendix full of facts about the body, some of which we know but more of which we have to look up, hence the value of the appendix.

The book is beautifully printed on excellent paper, well up to the standard we expect from Blackwells of Oxford.

E. Falkner Hill

FACULTY NEWS

We very much regret that owing to a misprint in the typescript report from the Royal College of Surgeons in the September issue of this Journal the undermentioned were reported as having been successful in the Diploma of Anaesthetics. They have in fact been successful in passing the examination for the Fellowship of the Faculty of Anaesthetists of the Royal College of Surgeons. While this is indeed the diploma of anaesthetics given by the College, the previous wording could obviously give rise to confusion with the conjoint diploma.

Ainley-Walker, J. C. S.
Anderson, J. L.
Brandstater, B. J.
Burkinshaw, Daphne
D'Bras, B. E. G.
Delaney, E. J.
French, O. H.
Genever, R. J.
Jolly, C. R.
Kaufman, L.
Keen, R. I.
Laurie Smith, N.
Lumb, Patricia Mary.
Marshall, M.
Merrifield, A. J.
Parker, Sheila Margaret.
Phillips, A. H.
Poon, Yee Kit
Prince-White, Freda Elizabeth.
Rolfe, M. G.
Schooling, Isabel Brenda.
Sims, A. J.
Thomson, T.
Webster, A. C.
Wise, R. P.
Wright, D. G. R.
Young, T. M.

Brit. J. Anaesth. (1956), **28**, 459

PHYSIOLOGY OF THE ADRENAL GLAND*

BY

J. H. BURN

Department of Pharmacology, Oxford

THE TWO PARTS OF THE GLAND

IT is now one hundred years ago since Vulpian observed that the adrenal medulla of the sheep developed a green colour in contact with ferric chloride, and, since the green colour was due to ferrous chloride, realized that the medulla contained a reducing substance. He found that the blood from the adrenal vein also reduced ferric chloride, and concluded that the reducing substance was liberated in the blood. He said, "This proves for the first time and in a decisive manner, the hypothesis which regards the suprarenal capsules as being like the glands termed vascular, glands pouring their products of secretion directly into the blood". Nine years later Henle described the characteristic brown-yellow colour which appeared when potassium dichromate was applied to the adrenal medulla, and which led to the description of the medulla as composed of chromaffin tissue.

In many vertebrates such as lampreys the cortex and medulla of the adrenal are distinct. Thus in *Petromyzon*, Giacomini (1927) described irregular bodies attached to the posterior cardinal veins which represent the cortex of the mammalian adrenal; then he described strands of tissue running along the large arteries which represent the chromaffin tissue, that is the adrenal medulla, of higher forms. In sharks the cortical substance is a single large body between the kidneys, while the chromaffin bodies are situated on both sides of the dorsal aorta and are arranged segmentally. In the human foetus and in the newborn baby there is a similar anatomical separation of cortex from tissue functioning as the medulla, for the organ of Zuckerkandl appears to be the main source of noradrenaline and adrenaline in early human life. This body, described by Zuckerkandl in 1901, is a mass of chromaffin tissue on the anterior surface of the aorta near the origin of the inferior mesenteric artery. This collection of cells on the aorta reaches its greatest development in children some months after birth and then it becomes fibrosed and atrophic.

West, Shepherd, Hunter and Macgregor (1953) compared the changes which take place during foetal life and after birth in the organs of Zuckerkandl with those in the adrenal medulla. They reached the general conclusion that the organs were the main site of formation of noradrenaline in foetal life, during which the adrenal medulla is immature. They examined the organs of Zuckerkandl and the adrenal medulla collected from a series of subjects 6 to 24 hours after death. Histologically the organs were found to

* Lecture given to the Scientific Meeting held by the Faculty of Anaesthetists in the Royal College of Surgeons on Saturday, May 5, 1956.

be mature at about 22 weeks of gestation and from then on did not change until some months after birth. At about 8 months there was a decrease in vascularity and in the size of the cells and an increase in fibrous tissue. The adrenal medulla began to develop only after birth. They found that the amount of noradrenaline increased steadily in the organs of Zuckerkandl from 15 weeks of foetal life until 2 months after birth, the total in the organs being appreciably greater than that in the adrenal medulla during this period. Thereafter the amount in the organs declined while that in the medulla rapidly increased.

Thus we see that ontogeny recapitulates phylogeny, and that in the early life of a man there is a stage where the cortex and the medulla are separate as they are throughout the existence of vertebrates lower in the scale of development. Occasionally the organ of Zuckerkandl in man does not become fibrosed and atrophic, but persists, and, indeed, may give rise to a tumour. Cases are on record in which all the signs of an adrenal medullary tumour were present, but on examination the surgeon found that the adrenal glands were normal; further exploration revealed a tumour of the organ of Zuckerkandl (Engel and v. Euler, 1950).

THE FUNCTIONS OF THE ADRENAL CORTEX

We thus reach the position that in the course of evolution chromaffin tissue and the tissue of the adrenal cortex, formerly two separate organs, have been brought together into one organ, the adrenal gland, and we have to find a reason for this conjunction if we can.

Knowledge of the adrenal medulla progressed rapidly after the observation of Oliver and Schäfer (1895) that an extract had an immediate and powerful action in raising the blood pressure. Knowledge of the cortex has accumulated much more slowly because the effects of its active principles are not so dramatic, and take time to demonstrate; they escaped notice.

In 1938 Selye and Schenker showed that young rats when placed in a refrigerator at a temperature of 2–5°C. were able to withstand this exposure to cold quite successfully. If, however, the adrenal glands were removed, then exposure to a temperature of 2–5°C. was rapidly fatal. Adrenalectomized rats, however, were enabled to survive for a longer time when they received subcutaneous injections of an extract of the adrenal cortex. In 1943 Vogt described a method of comparing the potency of different extracts of the adrenal cortex based on Selye and Schenker's findings, in which she showed that the mean survival time of adrenalectomized rats was proportional to the dose injected. Thus it was clear that active principles could be extracted from the cortex which enabled the young rat to resist exposure to low temperature.

The active principles

The active principles of the cortex which are found in the adrenal vein in man are believed to be three, namely, hydrocortisone, corticosterone and aldosterone. These are hormones with a steroid structure, much more complicated than that of noradrenaline and adrenaline. The first, hydrocortisone, represents 80 per cent, the second represents 20 per cent, and the third less than 1 per cent of the active substances liberated (Rukes, Orr, Forsham and Galante, 1955).

Glucocorticoid activity

These different substances all share the property of prolonging the life of young adrenalecomized rats when exposed to cold. This property depends on the rapid formation of carbohydrate from protein and is known as glucocorticoid activity. The usual method of examining an extract for glucocorticoid activity is to test its effect on liver glycogen in rats or mice from which the adrenals have been removed and which are without food and in which the liver glycogen is therefore very low (Reinecke and Kendall, 1942).

An example of an experiment is given in table I which shows that the increase in liver glycogen was related to an increase in urinary nitrogen in conformity with the conception that protein breakdown is the source of the new carbohydrate. The table also shows that the effect of the dehydrocorticosterone in increasing liver glycogen was much greater in animals given glucose. By tests of this kind it has been shown that cortisone and corticosterone are two or three times stronger than aldosterone (Schuler, Desaulles and Meier, 1954). The activity of hydrocortisone is likely to be similar to that of cortisone.

TABLE I
(From Venning, E. H., Kazmin, V. E., and Bell, J. C. (1946). *Endocrinol.*, **38**, 79)

Mice	Dehydro-corticosterone	Total urinary N	Total liver glycogen
12, without food	None	39 mg	5 mg
12, without food	300μg/mouse	71	12
12, 70 mg glucose	None	42	10
12, 70 mg glucose	300μg/mouse	75	210

The sodium-retaining property

Another property possessed by the adrenal cortex is that of controlling the excretion of sodium by the kidney. The muscular weakness of Addison's disease is well known to be relieved in many patients by the administration of sodium chloride, and it is therefore not surprising that it has been observed that the substances liberated in the adrenal vein have the property of diminishing the excretion of sodium. In adrenalectomized animals, however, there is not only an increased sodium loss, but there is a decreased loss of potassium due to increased reabsorption of potassium by the tubules of the kidney, and in consequence there is an increased plasma potassium. The control of the excretion of sodium and potassium by the hormones of the adrenal cortex can therefore be studied by a method described by Simpson and Tait (1952) in which they determined the ratio of sodium to potassium in the urine. For these experiments they injected young adrenalectomized rats with a solution containing known amounts of radio-active sodium (^{24}Na) and radio-active potassium (^{42}K), and then determined the amounts of these in the urine at the end of 2 hours. In one experiment the ratio was as high as 2.5 in the control animals, and it fell, in relation to the amount of desoxycorticosterone (or doca) which was injected, to 1.2 for rats receiving 2.8 μg doca. The ratio fell because the sodium

excretion was diminished and because the potassium excretion was increased.

While desoxycorticosterone or doca is not a substance liberated by the adrenal gland, the substance aldosterone is liberated by the gland and it has been found to be no less than 120 times as potent as doca (Speirs, Simpson and Tait, 1954). This remarkably high potency in diminishing sodium excretion and increasing potassium excretion is independent of water excretion, for aldosterone, unlike doca, does not cause water retention. The effect on sodium and potassium excretion is not confined to the kidney, but is exerted on the output of sodium and potassium in saliva and sweat also. As is well known, those who become acclimatized to the heat of tropical climates are able to sweat profusely without loss of sodium. It appears from the work in Ann Arbor by Conn and his associates (personal communication) that the reduced loss of sodium is due to a greatly increased secretion of aldosterone.

Action on eosinophil cells in the blood

Another property of the cortical hormones is that when released in the blood they cause a fall in the number of eosinophil cells in circulation. Since the physiological significance of this change is uncertain, this property is mentioned only because it may also be used to compare the different hormones of the adrenal cortex (Speirs and Meyer, 1951). Thus, aldosterone has from one-quarter to one-half the potency of cortisone, and cortisone is equal in action to hydrocortisone.

The anti-inflammatory action

The observations of Hench, Kendall, Slocomb and Polley (1949) showed that cortisone had a powerful effect in restoring the mobility of the joints in rheumatoid arthritis. This is generally regarded as an effect due to the dissolution of inflammatory exudate and to the disappearance of fibrous tissue around the joints, and is considered as one aspect of the action of cortisone in suppressing inflammatory processes. There seems to be no doubt that cortisone and hydrocortisone when given in large doses can lower the resistance of both animals and men to certain forms of infection. Thus it has been shown that cortisone enhances tuberculosis in animals and increases the mortality from it, and there is evidence of a similar effect in man. Robinson (1953) showed that cortisone greatly increased the severity of the infection which resulted from injecting rabbits with pneumococcus type I. All control rabbits survived for 10 days, whereas only 20 per cent of the rabbits injected with cortisone survived for this period. Among the control rabbits pneumococci appeared in the blood in small numbers and only for a short period. In the rabbits treated with cortisone or hydrocortisone there was an overwhelming blood infection at the end of 48 hours. At the site of inoculation the local pathological changes spread much more widely in the animals treated with cortisone, and the influx of polymorphonuclear leucocytes into the area in which the pneumococci were present was much slower.

Thus it is clear that the cortical hormones given in large doses may exert a harmful effect in certain infections. This does not exclude the possibility that smaller amounts may have the opposite effect. Lurie et al. (1951) observed that tuberculosis in rabbits was accompanied

by hypertrophy of the adrenal cortex, and that the degree of hypertrophy in naturally resistant rabbits was greater than in the more susceptible.

The anti-allergic action

Other effects of cortisone and of hydrocortisone have definite clinical value in suppressing various phenomena which may be grouped as allergic. In the condition known as status asthmaticus in which an asthmatic attack is of such severity that the usual remedies such as adrenaline and isoprenaline are without avail, the injection of cortisone, or of the adrenocorticotrophic hormone, ACTH, which causes the liberation of hydrocortisone from the adrenal gland, will save the patient's life. Cortisone is likewise useful in skin conditions such as lupus erythematosus which have an allergic basis.

THE RELEASE OF THE CORTICAL HORMONES

After this brief enumeration of the physiological processes in which the cortical hormones may play a part, and leaving aside consideration of the effects they may exert on the brain, which include alterations in appetite, in sleep, in motor activity and in personality, the question of the release of the hormones will be discussed.

The hormones of the adrenal cortex are released when the pituitary gland is removed, but the rate of secretion then remains constant (Vogt, 1954). The fluctuations which normally occur depend on variations in the output of ACTH from the anterior lobe of the pituitary which is in turn influenced by the amount of the cortical hormones in the blood. Thus Sayers and Sayers (1945) showed that when cortical steroids were injected the secretion from the adrenal cortex diminished because the output of ACTH fell. Similarly when the adrenals were removed the output of ACTH in the blood rose.

Much greater amounts of the cortical hormones are liberated in conditions of stress. The mechanism of the release again involves the anterior pituitary and is again set in motion by ACTH, but the output of ACTH is due to a different cause. In emotional stress, such as is evoked by fear, the appearance of adrenaline in the blood provides the main stimulus to the anterior pituitary to secrete ACTH. The chain of events is then as follows. Stimulation of hypothalamic centres, probably by still higher centres or perhaps reflexly, causes a discharge of impulses along the splanchnic nerves to the adrenal medulla with liberation of adrenaline. The adrenaline then stimulates the anterior pituitary to release ACTH, and this in turn releases the hormones of the adrenal cortex. There are, however, other forms of stress such as that caused by exposure to cold or by hypoglycaemia, in which emotion is not involved, where there is an increased secretion of ACTH whether adrenaline is circulating or not. Here it seems that the excitation of certain nervous centres, for example in the posterior part of the hypothalamus, leads to a discharge of ACTH directly, and so to a discharge of cortical hormones without the intervention of the adrenal medulla. This mechanism has been demonstrated by using animals in which the adrenal medulla of the two glands has been destroyed in a previous operation.

Under conditions of stress we may note that the hormones of the adrenal cortex and of the adrenal medulla support one

another. Thus hydrocortisone facilitates the conversion of protein to carbohydrate, while adrenaline breaks down glycogen to glucose. Again it has been demonstrated that cortisone (and therefore hydrocortisone) is required to maintain the blood-pressure-raising action of noradrenaline (Levine, 1952).

DISEASES OF THE ADRENAL CORTEX

There are several steroid substances capable of diminishing the symptoms of cortical deficiency. Thus testosterone administration leads to retention of sodium, but it leads to retention of potassium, nitrogen and phosphorus as well. Desoxycorticosterone has been much used in treatment, but it can cause hypertension due to sodium retention. By contrast cortisone does not have this effect and it allows hypertension to disappear. The substance which offers the greatest promise, however, is aldosterone, which removes all the symptoms of adrenal insufficiency, namely fatigue, nausea, anorexia, sleepiness, depression and the dyspnoea which occurs on making an effort. Finally aldosterone has been found to reduce or even remove pigmentation. There is no water retention after high doses, and no hypertension. There is increased excretion of potassium. Patients treated with aldosterone feel alert and are able to work hard.

Besides diseases due to cortical deficiency there are some due to hormone excess. Thus Cushing's disease is characterized by a moon face, the presence of striae on the abdominal skin, and by diabetes and hypertension. It is due to excessive production of hydrocortisone. This excess production follows the excessive production of ACTH, and the disease can be arrested by removing the pituitary gland. Another disease is the adrenogenital syndrome, in which the symptoms are due to the excessive production of androgenic substances by the adrenal. In this condition there is a deficient production of hydrocortisone, and because the amount of this in the blood falls the secretion of ACTH rises. The ACTH causes increased formation of C_{19} and C_{21} steroids. The adrenogenital syndrome is effectively treated by hydrocortisone, which diminishes the secretion of ACTH from the pituitary.

There are also cortical tumours in which there is an abnormally high production of aldosterone. These patients suffer from muscular weakness arising from a low plasma potassium. They have, on the other hand, a high plasma sodium. These changes occur because of the action of the aldosterone on the kidney, which results in diminished urinary excretion of sodium and increased urinary excretion of potassium. There is no oedema. The high plasma sodium is accompanied by a high plasma bicarbonate, and the pH of the blood may be 7.6, which is more alkaline than usual. The blood pressure is usually raised. All these symptoms disappear on removal of the tumour. It may be noted in conclusion that the secretion of aldosterone by the adrenal cortex does not depend on the output of ACTH from the pituitary anterior lobe.

CHANGE IN MEDULLARY FUNCTION

What has been said so far affords no clue to the reason for the collection of chromaffin tissue throughout the body to a position in which it is surrounded by the

adrenal cortex. As yet we cannot explain why the cortex surrounds the medulla in the adult mammal. It is, however, interesting to observe that in man, as the adrenal medulla of the young child takes over the function of the organ of Zuckerkandl, there is a change in the amine which is formed from noradrenaline to adrenaline. Table II shows figures given by Shepherd and West (1951) for the amounts of the two amines at different times after birth. In nearly all adult mammals the greater part of the medullary amine is adrenaline with the exception of the blue whale in which 83 per cent of the amine was found to be noradrenaline.

TABLE II

Amines in the human adrenal medulla
(Shepherd and West, 1951)
μg per g fresh tissue

Age	No. of subjects	Noradrenaline	Adrenaline
Under 70 days	25	30	2
0.5–2.5 years	3	100	100
Adult	31	31	209

Adrenaline is formed from noradrenaline by the substitution of a $-CH_3$ group for hydrogen in the $-NH_2$ group. This change has been demonstrated in the perfused adrenal gland of the dog, and it has been studied in minced adrenal tissue. When this is incubated together with adenosine triphosphate to supply energy, noradrenaline is converted to adrenaline. This work was done by my colleague Miss Bülbring (1949), and perhaps the most interesting feature of her very careful observations was that the conversion of noradrenaline to adrenaline was far greater if the adrenal glands were removed from the dog or the cat after stimulating the splanchnic nerves for 30 minutes. It appeared that nerve stimulation, which would liberate adrenaline into the blood stream, had also increased the activity of the methylating mechanism in the glands.

The importance of the change from noradrenaline is very great. In the first place noradrenaline has little or no power to cause a discharge of ACTH from the anterior lobe, and without adrenaline the power to augment secretion of cortical hormone in times of stress would be greatly reduced.

In the second place adrenaline is far more efficient to discharge the functions required in time of stress than is noradrenaline. Thus noradrenaline has been shown by Trendelenburg (1953) to have only one-fifth of the hyperglycaemic action of adrenaline, so that in the absence of adrenaline not only is the conversion of protein to carbohydrate less but the conversion of glycogen to glucose is also greatly reduced.

ACTIONS OF NORADRENALINE AND ADRENALINE

The action on the circulation.

A further difference between the two amines is in their vascular action. Adrenaline causes vasoconstriction in the skin and in the intestinal region, but in moderate amounts it causes dilatation of the muscle vessels. This dilatation is of obvious value during an emergency when a large blood supply to the muscles is required. Noradrenaline causes constriction in the muscle vessels. This difference can be easily shown by the method described by Dale and Richards (1918). They prepared cats by cutting the sciatic nerve to one hind leg in an aseptic operation, and some days later anaesthetized the cat with ether and

recorded the volume of the hind leg by enclosing it in a plethysmograph. When adrenaline was slowly infused into a vein the limb volume increased and as a consequence the blood pressure fell. It has been shown that in the same circumstances the infusion of noradrenaline caused a fall in the limb volume and a rise in blood pressure (Burn and Hutcheon, 1949).

The observations of Goldenberg and his colleagues (1948) suggest that the same difference between the two substances is found in man, for when they compared intravenous infusions of noradrenaline with infusions of adrenaline they observed that with noradrenaline there was a rise in the total peripheral resistance which was not seen with adrenaline. With moderate rates of infusion of noradrenaline, therefore, a rise of blood pressure occurs which is absent when similar amounts of adrenaline are infused, and it is therefore apparent that noradrenaline is preferable to adrenaline for raising the blood pressure. This preference for noradrenaline is supported by the action on the heart. When the two substances are compared on the isolated heart there is not a great difference between them. Noradrenaline is quite as powerful as adrenaline, if not slightly more powerful, in increasing the force of the beat, and, though it increases the rate of the heart less than adrenaline does, the difference is not great. But in the whole animal, where the cardiovascular reflexes exert their effect, noradrenaline has much less action on heart rate. Indeed, in man, Barcroft and Swan (1953) have shown that during the infusion of noradrenaline the heart rate is slowed, while during the infusion of adrenaline it is increased. The slowing is a consequence of the rise of blood pressure, which produces an increased vagal tone. A similar slowing occurs in the dog when adrenaline is infused provided that the amount is sufficient to raise the blood pressure.

The action on ganglia.

One of the troublesome features of the use of noradrenaline for slow intravenous infusion or as an intravenous drip to raise the blood pressure, is that once the blood pressure has been restored to the normal value, it is not always easy to discontinue the drip, for when it is discontinued the blood pressure often falls to a very low level, and the drip must then be continued for a longer time. This is due to an effect of the noradrenaline on the ganglia of the sympathetic chain. The constrictor impulses from the vasomotor centres in the medulla and the spinal cord leave the cord in the preganglionic fibres which terminate in the sympathetic ganglia. They transmit their impulses to the cells in the ganglia which give rise to the postganglionic fibres which then pass to the blood vessels. Adrenaline was shown by Marrazzi (1939) to have an inhibitory effect on the transmission of impulses in the ganglia from the preganglionic terminations to the postganglionic cells. He stimulated the preganglionic fibres and recorded the action potential in the postganglionic fibres, and showed that this action potential was reduced in size by the injection of adrenaline. Miss Bülbring and I (Bülbring and Burn, 1942) studied this effect by a different method, and discovered that adrenaline had a double action. We perfused the hinder part of a dog completely detached from the fore-

part, using two separate perfusion systems. The blood delivered by a pump in one system perfused the vessels going to the spinal cord and the sympathetic ganglia. The blood delivered by a pump in a second system perfused the vessels of one hind leg. The spinal cord and sympathetic ganglia were connected to the hind leg only through the nerves. It was then possible to stimulate the preganglionic fibres of the sympathetic chain and record a constriction of the vessels of the hind leg. When adrenaline was added at a steady rate to the blood perfusing the sympathetic ganglia at a time when no adrenaline was present, the effect of preganglionic stimulation (seen as constriction in the hind leg) was greatly increased. For example, the steady addition of 4 μg per minute to a reservoir containing 600 ml blood caused such an increase. When, however, the adrenaline inflow was raised to 10 μg per minute, the opposite effect was observed, and the vasoconstriction produced in the hind leg by preganglionic stimulation diminished until it almost disappeared.

In order to demonstrate conclusively that these effects were produced by adrenaline in the ganglia, and not elsewhere, Miss Bülbring (1944) carried out experiments in which she perfused the superior cervical ganglion and recorded contractions of the nictitating membrane; this is innervated by postganglionic fibres. The contractions she obtained by stimulating the preganglionic fibres with submaximal stimuli were increased by the injection of small amounts of adrenaline into the ganglion and diminished by the injection of larger amounts.

From the observations of Marrazzi and those just described there is no doubt that adrenaline, in concentrations which are not very high, can paralyse the transmission of the impulses which normally maintain arterial tone, the site of the paralysis being the ganglia. Hutcheon (1950), working in my department at Oxford, has shown that noradrenaline has the same action, though his observations do not show whether noradrenaline is more or less powerful than adrenaline in this respect. The results indicate that when an intravenous drip of either adrenaline or noradrenaline is given to a patient the constrictor action on the blood vessels, which raises the blood pressure, is accompanied by a block of sympathetic impulses, which are not transmitted through the ganglia. When the drip is arrested the vessels dilate and the blood pressure falls before the block has gone. It is therefore necessary to spend a considerable time in stopping the drip, reducing it, for example, by as little as 10 per cent at a time. If this is done the block has a chance to disappear, and then the sympathetic nerves take over vascular control once more.

I often think I would like to suggest the use of a drip of vasopressin in cases where it is difficult to interrupt a noradrenaline drip. Vasopressin has no blocking effect on the ganglia and there is no abrupt fall of blood pressure when a vasopressin drip is stopped. However, the argument is always used that vasopressin causes coronary constriction and would therefore be dangerous. To this it can be replied that a vasopressin drip works well in the cat or the dog, and that the effects of coronary constriction are not seen. Certainly in those cases of which I have heard, where a noradrenaline drip has had to be maintained for several days, it would seem

reasonable to try to replace the noradrenaline by vasopressin, perhaps only partly, and of course gradually. A study of the effect of a vasopressin drip in patients with low blood pressure might yield useful results.

LIBERATION OF NORADRENALINE FROM THE ADRENAL GLAND

In 1949 Miss Bülbring and I showed that when the splanchnic nerves were stimulated in the cat both adrenaline and noradrenaline were liberated from the adrenal medulla. The proportion of the two amines liberated varied greatly in different cats, there being more adrenaline than noradrenaline in some and less in others. The fact that noradrenaline is liberated by splanchnic stimulation has given rise to speculation whether it has a special function not shared by adrenaline. Hitherto no answer has been found, for while there are several properties possessed by adrenaline which noradrenaline has not got, there are none yet discovered of which the reverse is true if we except the greater pressor action of noradrenaline. There is, however, evidence that stimulation of the hypothalamus at one point causes the release of mainly noradrenaline from the gland, whereas stimulation at a different point causes the release of a large amount of adrenaline as well (Folkow and v. Euler, 1954). Furthermore there appear to be cells in the adrenal medulla which contain noradrenaline and others which contain adrenaline. This statement makes one wonder how the evidence for it was obtained, and it is worth while explaining that the work was done by Eränkö (1955), who is a Finn. He used histochemical methods which reveal brightly fluorescing cell groups in the adrenal medulla against a dark background. He made estimates of the proportion of fluorescing tissue as a percentage of the whole medulla, and found that it was similar to the proportion of noradrenaline as a percentage of the total amines in different species. In the cat and the hamster he made serial sections of fresh adrenal glands. Every other section was fixed in formalin and examined for the distribution of fluorescing islets, while the alternate sections were freeze-dried. From the freeze-dried sections pieces were dissected which, judging from the neighbouring sections, contained the fluorescing cells. Eränkö found that a piece with much fluorescing tissue always contained a higher proportion of noradrenaline than a piece from the same section with little fluorescing tissue. He took his observations to mean that some cells of the adrenal medulla contained much adrenaline and little noradrenaline, while others contained noradrenaline only. His work seems to have been done very beautifully.

It is perhaps not surprising that there should be areas in the medulla containing noradrenaline distinct from other areas which contain both amines but chiefly adrenaline. If we consider the adrenal medulla as having at least two functions—first, the formation of noradrenaline from dopamine (or hydroxytyramine) and, second, the formation of adrenaline from noradrenaline—it is likely that this second function is carried out by different cells from those which carry out the first. It is therefore not surprising that the amines differ in their distribution in the medulla. This difference need not imply that their

discharge is separately controlled. But Folkow and v. Euler's observations, indicating that stimulation at one point of the hypothalamus liberates noradrenaline while stimulation at a second point liberates mainly adrenaline, do support the hypothesis of a separate control of the release of the two amines, and if this hypothesis is established it will be important to know the purpose of the release of noradrenaline alone. Present knowledge does not reveal this, unless it be that noradrenaline assists the normal sympathetic tone to keep the blood pressure high.

PROBLEMS REMAINING

Of the working of the adrenal gland much remains to be discovered. We have no idea of the mechanism of the anti-allergic action and of the anti-inflammatory action of the cortical hormones, and of course very little idea of how these hormones are acting when they convert protein to carbohydrate or when they absorb sodium in the kidney tubules. Knowledge, however, expands steadily, and we have learnt in the last few years, for example, that when adrenaline converts glycogen to glucose, it does so by increasing the amount of the enzyme phosphorylase (Rall, Sutherland, and Wosilait, 1956). That is an important step forward.

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MODE OF ACTION OF NEUROMUSCULAR BLOCKING AGENTS*

BY

W. D. M. PATON

Department of Pharmacology, Royal College of Surgeons of England

TEN years ago, it would have been fairly easy for a pharmacologist to give an account of how drugs act which produce neuromuscular block. But two main developments have made the story more complicated. First, among such drugs, substances of different and indeed of diametrically opposed action are now known. Secondly, with the clinical exploitation of curare and similar compounds, the anaesthetist now asks much more searching questions, such as why a paralysis is sometimes abnormally prolonged, what happens when different relaxants are combined, or how different clinical conditions influence their action. This paper, therefore, will discuss some of those results or lines of investigation in the laboratory which throw most light, or may come to throw light, on these everyday practical demands.

COMPETITION AND DEPOLARIZATION BLOCK

Our picture of neuromuscular transmission, now, is the following: the nerve impulse releases acetylcholine at the nerve endings; the acetylcholine then depolarizes the endplate region simply by making a sort of physiological "short circuit" across the membrane there (Fatt and Katz, 1951); the local negativity so set up then excites the adjacent muscle membrane, leading to a propagated action potential and to muscular contraction; the acetylcholine is meanwhile rapidly destroyed by the cholinesterase present, so as to prepare for the next impulse. Substances such as curare simply act by being sufficiently like acetylcholine to have an affinity for the specific receptors normally receiving acetylcholine, but so unlike acetylcholine that they cannot activate the receptors. They thus "compete" with acetylcholine, just as (to use a frivolous analogy) a very fat man in a revolving door, with an "affinity" for the door yet incapable of passing through it, prevents those of more normal size from using it. Such a view of curare's action is very satisfactory: it explains all the forms of curare's antagonism to acetylcholine, the effects of anticholinesterases, and why quaternary salts almost always have a neuromuscular action.

But the picture became more complicated again when it was recognized that another type of neuromuscular block existed, which can now be termed block by depolarization. This was, indeed, indicated many years ago, when eserine and neostigmine were first studied. But it

* A paper given at the World Congress of Anaesthesiologists, Scheveningen, Holland, in September 1955.

became important with decamethonium; and the clinical usefulness of such block is now fully established with suxamethonium. The first analysis of depolarization block was made using decamethonium; although it is now less commonly used than suxamethonium, it is in some ways more convenient to study, since its destruction in the body does not complicate the experiments. But precisely analogous findings have been made with suxamethonium and with acetylcholine itself.

Depolarization block can be introduced in a general way by listing (table I) the differences which were found to exist between d-tubocurarine and decamethonium (reviewed by Paton and Zaimis, 1952). It was disconcerting to find two substances, both neuromuscular blocking agents in the classical sense, and therefore presumably both acting within the same extremely restricted area, which yet differed in almost every detail. The most fundamental of these differences seemed to be that decamethonium, like acetylcholine, could specifically depolarize and excite the motor endplate. It is rather remarkable

TABLE I

Test	d-Tubocurarine	Decamethonium
(1) Muscle selectivity:		
(*a*) among species	Sensitivity of rat > mouse > rabbit > man and cat.	Sensitivity of man and cat > rabbit > mouse > rat.
(*b*) within species:		
cat	Respiration and soleus more sensitive than tibialis.	Tibialis more sensitive than respiration and soleus.
man	Laryngeal, pharyngeal, and ocular muscles outstandingly sensitive compared to skeletal muscles.	Laryngeal, Pharyngeal, and ocular muscles only moderately sensitive, compared to skeletal muscles.
(2) Effect of substances raising threshold of end plate to acetylcholine (d-tubocurarine, gallamine, pentamethonium, ether anaesthesia).	Potentiation.	Antagonism.
(3) Muscle stimulation.	Nil or trivial in all species tested.	Fasciculations, with repetitive firing, in cat muscle and in human muscle. Contractures of denervated cat muscle and avian and frog muscle.
(4) Tension during a tetanus of the motor nerve.	Rapid decay.	Sustained.
(5) Miscellaneous:		
(*a*) potassium	Antagonism.	No effect.
(*b*) previous tetanization of motor nerve	Antagonism.	No effect.
(*c*) anticholinesterases	Antagonism.	Little effect, occasionally feeble potentiation or antagonism.
(*d*) m-OH-phenyldimethylethyl ammonium (Ro 3198; Tensilon)	Antagonism.	No effect or potentiation.
(*e*) effect in myasthenia.	Hypersensitivity.	Normal sensitivity or resistance.

how the spatial distribution of the endplate depolarization in a muscle after decamethonium is indistinguishable from acetylcholine (fig. 1).

But the discovery that decamethonium can stimulate a muscle does not, at first sight, explain how it produces neuromuscular block. One might think, indeed, that it would tend to prevent block and to help acetylcholine perform its tasks more effectively. Two immediate theories might be made.

(*a*) The first, which one can call the "concealed competition" theory, is that, although the depolarization is of interest, yet the fundamental action of decamethonium is still one of competition, preventing acetylcholine from producing at the endplate region a response (endplate potential or e.p.p.) big enough to excite normal muscle. Such a theory is intrinsically unlikely, for it would require the drug (already known to be acetylcholine-like and to summate with acetylcholine) to have at the same time an antagonism to acetylcholine; and this antagonism must be sufficient not merely to reduce the endplate potential as far as curare does, but a good deal further, so as to overcome the assistance which decamethonium, by partially depolarizing the endplate, has already given to the endplate potential.

(*b*) It might be proposed, on the other hand, that when neuromuscular block is established by decamethonium, then the endplate is so profoundly depolarized that acetylcholine released by a nerve impulse can do nothing more (the "total depolarization" theory). Again, there is at once a difficulty; for, if this were the case, why does not the muscle fibre become continuously activated by such a maximally excited endplate? Yet we know that, in fact, the stimulant phase of the action of such drugs is transient.

The problem has been analysed electrophysiologically in some detail (Burns and Paton, 1951); but we need not discuss the full evidence. A single observation disposes of both these suggestions, and provides a key to the true explanation (fig. 2).

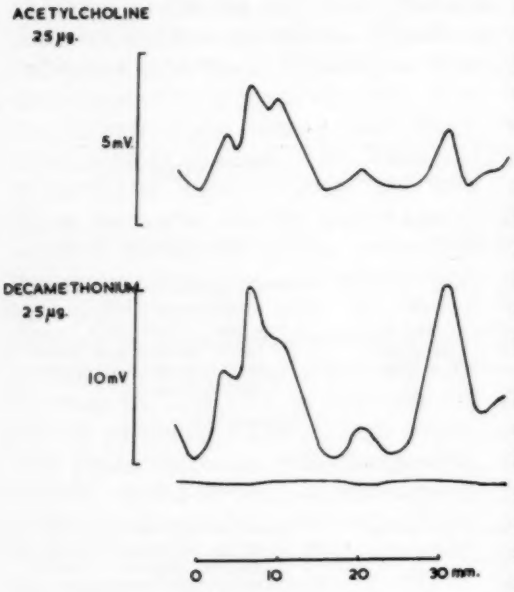

FIG. 1

Records of the distribution of potential along brachio-radialis muscle in the cat (a) normal (lowest tracing); (*b*) after 25 µg decamethonium intra-arterially (middle tracing); (c) after 25 µg acetylcholine intra-arterially (top tracing).

This muscle has a complicated system of endplates, which is mapped out by the depolarization produced by the two drugs. Although acetylcholine has a less intense depolarizing action than decamethonium, because it is destroyed by cholinesterase, the selective actions of the two drugs on endplate regions are exactly parallel.

(From Burns and Paton (1951) by permission of the *Journal of Physiology*)

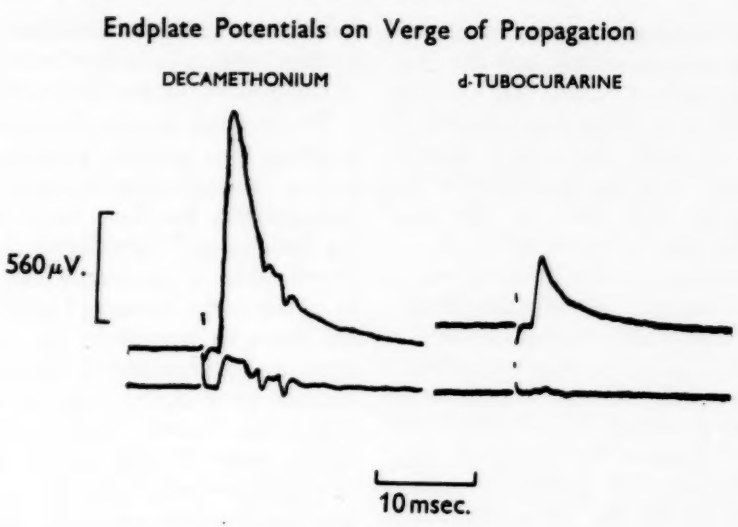

FIG. 2

Records of endplate potentials in response to excitation of the motor nerve of the cat's gracilis. In each tracing, the upper record is taken with an electrode directly over the endplate, the lower record with an electrode 2 mm away; the lower record serves to show that the muscle is just on the verge of being excited by the endplate potential, as indicated by the irregular abortive "spikes".

The lefthand tracings were obtained by allowing a muscle to recover from a large dose of decamethonium until the verge of propagation was reached. The righthand tracing was obtained after full recovery from decamethonium, using the same method on the same endplate region with d-tubocurarine.

(From Burns and Paton (1951) by permission of the *Journal of Physiology*)

It depends on finding, at the endplate region, the size of endplate potential which is just on the threshold of exciting the muscle fibre. d-Tubocurarine does not affect the muscle membrane electrically, so that the e.p.p. obtained with it measures the normal "propagation threshold". With decamethonium, however, even though the endplate potential starts from a raised "base-line" of pre-existing depolarization, yet it has to be up to three times greater to excite the muscle than with d-tubocurarine. If bigger endplate potentials can be seen after decamethonium, then we must abandon the theories that it acts like d-tubocurarine (which would require the same sized potentials or even smaller ones, according to the degree of endplate depolarization), or that the endplate is totally depolarized (which would abolish the potentials). Further, we have a demonstration of the main cause of block. It is that, after decamethonium, the muscle fibre has become refractory to electrical stimulation, either by the endplate potential or by externally applied shocks. Hence an endplate depolarization, which in the normal or curarized muscle would be fully adequate to excite, comes to be ineffective, since it cannot stir into

activity the inexcitable membrane around it. It is important to realize that this electrical inexcitability does not develop immediately. Only if the depolarization is prolonged for more than a few seconds does it occur. It is the persistence of the depolarization that leads to the local inexcitability and hence to the block.

We reach the position, then, of recognizing two types of neuromuscular block: one due to competition with acetylcholine, the other due to the development of electrical inexcitability of the muscle round the endplate as a result of a persistent endplate depolarization. Reflecting on these two mechanisms, it is possible to understand fairly readily the salient differences of detail between d-tubocurarine and decamethonium (Paton, 1951).

I would like to digress here for a moment on to the problem of how to diagnose what type of block exists. For some time what one can call the general "clinical" picture has often been used. But I am coming to suspect that this is not good enough, particularly if one or two signs alone are taken. Suppose one draws an analogy between assessing the state of the neuromuscular junction and, for example, diagnosing a case of thyrotoxicosis; then features such as the tetanic response, or the proportionate effect on the respiratory muscles, or the sensitivity to anticholinesterases correspond to suggestive (but not decisive) signs such as loss of weight or shaky hands. But the *specific* diagnosis of thyrotoxicosis, especially in doubtful cases, rests on the basal metabolic rate and on the iodine uptake by the gland; so also the *specific* diagnosis of the neuromuscular state rests on determining the electrical conditions at the endplate. I shall try to indicate later that this could be done, with a little development, almost as easily as taking an electrocardiogram.

We have not discussed one outstanding problem. The fact that prolonged excitation or depolarization produces electrical inexcitability has long been recognized, for instance as "cathodal block" of peripheral nerve. It has usually been presumed to be due to the leakage of potassium from the nerve or muscle at the depolarized area, and Burns and I invoked such a mechanism to explain some of our results. Perry and Zaimis (Zaimis, 1954) have shown (with ^{42}K) that there is an increase (up to 30 per cent) in the flux of potassium from perfused muscle under the influence of decamethonium. But such an experiment only measures the traffic in one direction, and two important questions remain. Does the muscle actually *lose* significant amounts of potassium; for instance, is the loss big enough to produce a rise in blood potassium? And do local circulatory conditions, which might influence its accumulation in the tissue spaces, influence depolarization block? In some recent experiments, measuring the absolute amounts of potassium in the blood and in the effluent from perfused muscles, I have found that substantial amounts of potassium are mobilized. With the cat's isolated perfused gastrocnemius (fig. 3) the release amounts to about 1 per cent of the potassium in the muscle. It tends to fall away with repeated injections, or during a continued infusion. If the flow of perfusate is very fast, the rise in concentration of potassium in the effluent is correspondingly reduced; if the flow is slowed, it rises, although it does not rise above a certain limit. These experiments

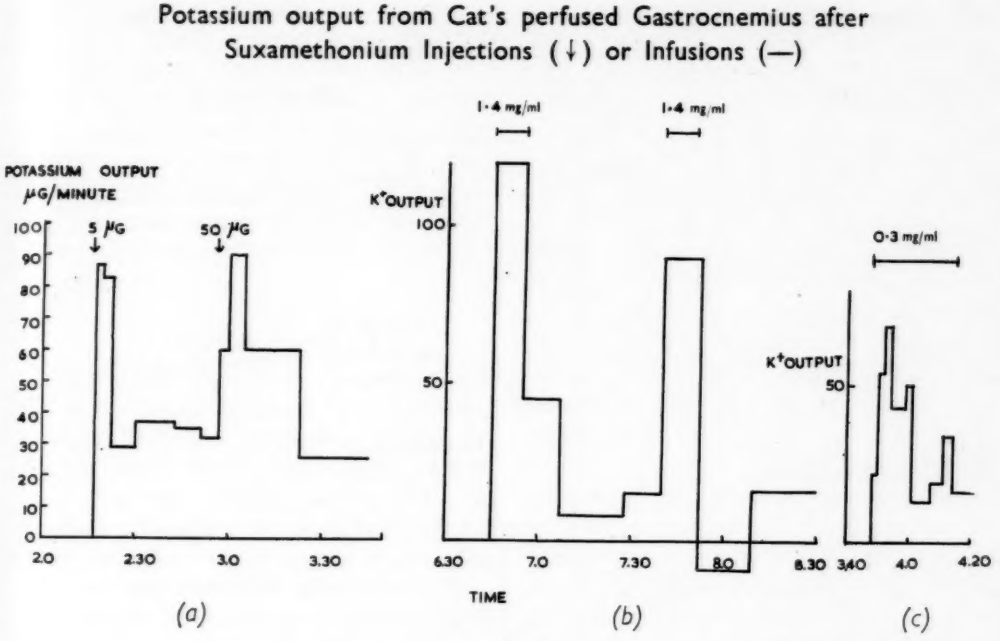

FIG. 3

Results of experiments on the output of potassium from an isolated perfused gastrocnemius muscle of the cat.

In (*a*) single injections of 5 μg and 50 μg suxamethonium were given.
In (*b*) an infusion of suxamethonium, 1.4 mg/ml, was given twice, for 10 minutes each time.
In (*c*) an infusion of suxamethonium, 0.3 mg/ml, was given for a period of 30 minutes.

show that release takes place unequivocally from the muscle itself.

In the whole animal the total release is sufficient to raise the plasma potassium levels very substantially (fig. 4).* Since potassium release can occur with other conditions, notably sympathetic activity or adrenaline release, it is necessary to keep the animal on artificial respiration to prevent asphyxia. Further, when using suxamethonium, it might be objected that the rise in plasma potassium was due to its ability to stimulate sympathetic ganglia (although this is only a feeble action). This can be excluded in two ways. Firstly, decamethonium, which lacks any ganglion-stimulant action, is as effective in raising the plasma potassium. Secondly, if the animal is eviscerate (so removing the liver from which adrenaline mobilizes potassium), suxamethonium is still effective. Indeed, it is highly potentiated, so that a several times smaller dose is required to produce the same neuromuscular effect as in the normal animal.

* Since this work was done, the paper by H. Klupp et al. (*Arch. int. Pharmacodyn.*, **98**, 340–354, 1954), was drawn to my attention. These authors found that in dogs, suxamethonium and decamethonium could increase the plasma potassium by up to 30 per cent; that d-tubocurarine (except in large doses) was free of this action, but could antagonize potassium release by suxamethonium and decamethonium; and that potassium release from perfused hindlimbs could be achieved.

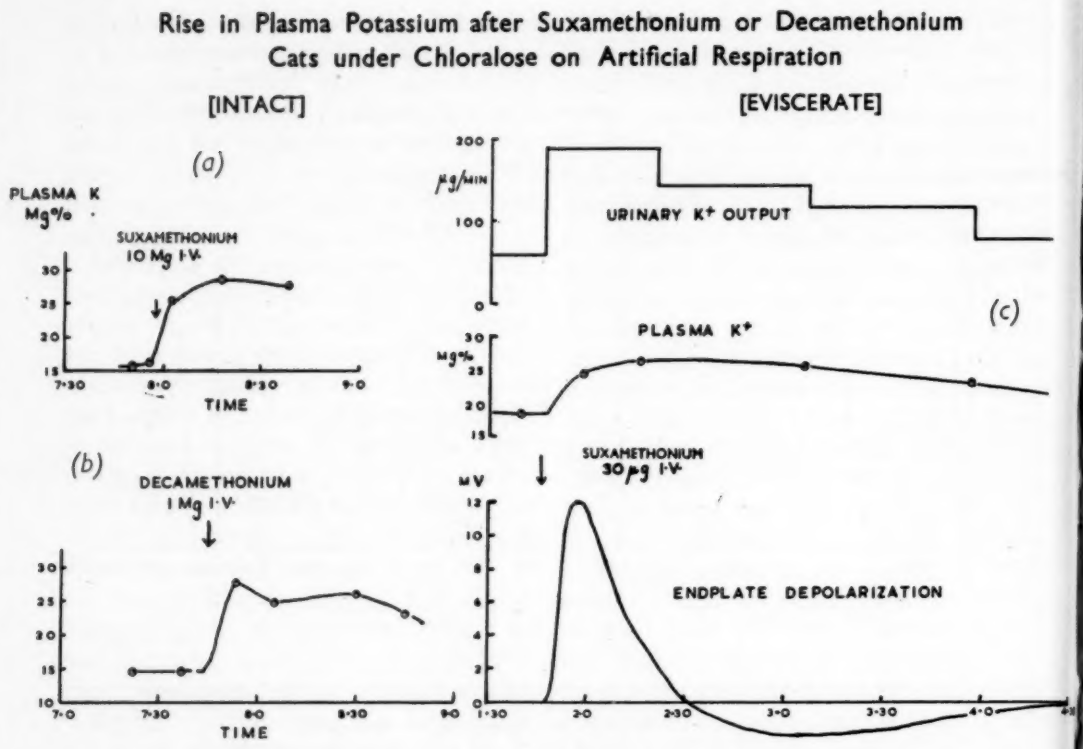

FIG. 4

Results of experiments on the change in plasma potassium concentration in cats anaesthetized with chloralose and on artificial respiration after decamethonium or suxamethonium.

(*a*) Effect of 10 mg suxamethonium on plasma potassium level.

(*b*) Effect of 1 mg decamethonium on plasma potassium level. The response is as great, although decamethonium is totally devoid of any sympathetic stimulant action.

(*c*) Effect of 30 µg suxamethonium in a cat eviscerated to exclude participation by the liver in the mobilization of potassium. The middle tracing shows the changes in plasma potassium, which outlast considerably the endplate depolarization (lower tracing). In this animal there was a satisfactory urine flow, and the increase in urinary potassium (upper tracing) corresponded with the rise in plasma level.

This suggests that defect of liver function may influence considerably the destruction of suxamethonium in the body.

The fact that these ionic movements are so big means that during, and after, a block by a drug depolarizing the endplate, the ionic concentrations either side of the muscle membrane must be significantly altered. The implications of this for the state of block are not simple, but it is clear that the reaction of the endplate and of the muscle membrane adjacent will be radically conditioned by them. Their existence supports, in addition, the suggestion made some time ago that the relationship between bloodflow and neuromuscular block with decamethonium (Churchill - Davidson and Richardson,

1952) is related to potassium release into the intercellular spaces (Paton, 1952). It is worth noting, too, that the duration of elevation of plasma potassium considerably outlasts that of the endplate depolarization, and, a fortiori, that of the block itself. The attractive transience of suxamethonium's relaxant action may hide a more prolonged effect in the body as a whole.

MIXED BLOCK

We have discussed neuromuscular block so far in terms of two contrasted types: that by competition where the action of the transmitter is antagonized; and that by depolarization with the development of electrical inexcitability at the endplate, where a transmitter-like action is exerted but for an abnormal time. But there is evidence that neuromuscular block of an intermediate kind may exist, in which a depolarization may take place initially and pass off, leaving nevertheless a state of block, now competitive in character. Drugs which first stimulate and then desensitize the tissue both to their own action and to that of similar substances have been known since Straub (1907) first showed the phenomenon for the action of muscarine on Aplysia heart. Nicotine, in its action on autonomic ganglia, is a notable example; and many sympathomimetics amines have the characteristic sequence of sympathomimetic followed by sympatholytic action. Among drugs active on the endplate a similar type of action is described for some of the aliphatic quaternary salts studied by Dallemagne and Phillipot (1951), Ginzel et al. (1952) and Zaimis (1953). With decyltrimethylammonium it has, indeed, been verified electrically that this drug will produce an endplate depolarization, which may then disappear, leaving a block of competitive type behind (Paton, 1951).

But these observations are not on drugs in clinical use, and we must ask whether there is any possibility that the relaxants actually employed by the anaesthetist might come to behave in a similar way. Is it possible, in fact, that suxamethonium or decamethonium might come, perhaps under special conditions, to lose their characteristic action and resemble curare-like drugs? At present no decisive evidence exists. But there are several reasons which indicate, on pharmacological grounds, that such a development might occur.

First, it is of interest to compare the structures of the compounds whose action is fairly well understood from the point of view of their lipophilic tendency. Data do not exist, and indeed are not easy to obtain, giving quantitative measurements of this sort. But one can estimate it in a simple way by enumerating the carbon atoms in each molecule (lipophilic) and comparing them (table II) with the number of quaternary groups (hydrophilic). One can then see how, with increasing proportions of hydrocarbon to hydrophilic material, the mode of action moves from depolarization through mixed action to pure competition. The point is, of course, one which Bovet (1951), in his classification of lepto- and pachycurares, has already taken up. But here I am trying to estimate, not the shape of the molecule, but its tendency to be fixed in a fatty or a watery phase—i.e., its partition coefficient. The scheme suggests that drugs with some measure of hydrocarbon loading may

TABLE II

Relation between type of neuromuscular action and ratio of lipophilic atoms (carbon) to hydrophilic atoms (nitrogen).

(Data from Ginzel et al., Dallemagne and Phillipot, Zaimis, and unpublished)

Compound	Action		C atoms / N atoms
	Depolarization	Competition	
T.M.A. (tetramethylammonium)	++		4
Acetylcholine	++		5
Suxamethonium	++		5
Decamethonium	++	(±)	8
Amyltrimethylammonium	++		8
Decamethonium (Me 2 : Et 1)	++	+	9
Decamethonium (Et 2 : Me 1)	++	++	10
Tridecamethonium	+	+	9.5
Gallamine	±	++	13
d-Tubocurarine	±	++	19
d-Tubocurarine methyl ether	−	++	20
Neostigmine	++	+	5.5

(through their lipoid affinity) develop an attachment to the membrane of a kind different from, additional to, and interfering with, the attachment which leads to endplate activation. For instance it might be essential, for normal activation, that a chemical bond involved be rapidly made and broken, or that the molecule has to move across or through the membrane; fixation of the molecule by its hydrocarbon content to adjacent lipoid regions of the membrane could well interfere with such a process. Now although suxamethonium and decamethonium are less lipophilic than the other compounds, they are not much less so. It seems possible, therefore, that a latent competitive element in their action might develop, particularly if their action were sufficiently prolonged, or if they were given in large doses, so that lipoid fixation could occur.

Secondly, we may note that continuous exposure even to normal naturally occurring molecules such as histamine, adrenaline or acetylcholine, may induce "accommodation" to their effects such that a state of relative refractoriness to excitation by them develops (Barsoum and Gaddum, 1935; von Euler, 1955; Douglas and Paton, 1954). Whether Straub's (1907) explanation (that the action of such drugs depended on the ratio between extracellular and intracellular concentrations, and hence could be diminished by passage of the drug inside the cell) is correct we do not know; but again it would lead us to expect a change in the character of the action of endplate stimulants with passage of time.

The possibility for explaining this accommodation that now interests me is that it is changes in potassium (and perhaps sodium) concentrations at the endplate region which can alter the responses of the endplate. We know that raised potassium levels can render tissues inexcitable, and there are indications that low potassium levels can increase the stimulant effect of some ganglion-blocking drugs (Perry and Reinert, 1954). The ionic consequences of a long-continued depolarization might well condition the endplate so that the

response to acetylcholine diminished, and propagation became more difficult.

Thirdly, we must remember that when depolarizing drugs are given after a previous dose of a competitive drug (for instance suxamethonium after d-tubocurarine) they lose some of their characteristics and come closer to being competitive in type.

It seems possible, therefore, from the purely pharmacological standpoint, that the depolarizing drugs, particularly if given (*a*) for a long time, or (*b*) in big doses, or (*c*) in conjunction with competitive drugs, may themselves lose some of their characteristic features and come to behave as being at least in part competitive, or may come to alter the responses of the motor endplate to other drugs.

Now from the practical point of view it is obviously impossible to predict what will happen. Would it be possible to assess the neuromuscular state of a patient during surgical anaesthesia? Until recently this might have been thought impracticable. But in fact the electrical changes in a muscle, produced by the localized endplate depolarizations throughout it, are quite gross and can be picked up by a diffuse nonpolarizable electrode placed, not accurately on an endplate region, but anywhere on the main body of a muscle, and recorded on a simple galvanometer. Unfortunately percutaneous recording in man is complicated by potentials existing in the skin. But these can be countered, or non-polarizable electrodes suitable for hypodermic use can be developed. Figure 5 shows the type of record obtained, with graded doses in the cat. There is no reason

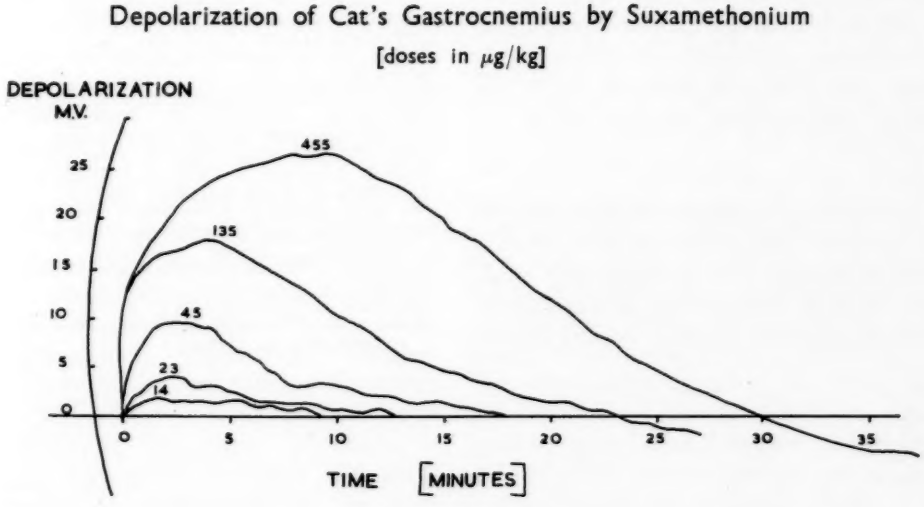

FIG. 5

Records of the depolarization of the gastrocnemius muscle of a cat anaesthetized with chloralose. The records were obtained with an electrode placed on top of a small saline-filled swab of cotton wool placed on the belly of the muscle, without localizing the endplate regions. The doses of suxamethonium, given intravenously, are marked opposite the corresponding tracing.

why an anaesthetist should not record for himself, if he wishes, similar tracings during an operation.

The figure allows me to bring out one last point. Study of muscular activity alone gives an incomplete picture of the course of events at an endplate. Before block begins, changes occur; when paralysis of transmission is complete, the drug's fundamental action can still be made more intense; and after recovery, there is a considerable interval before the endplate is normal. If one has then a record of (say) paralysis and recovery of the respiration, one must imagine also on the record a short "nose" corresponding to the beginning of the drug's action, a big "back" corresponding to the course of its action during the period of complete paralysis, and a long pharmacological tail after apparent recovery had occurred. It would be one of the uses of recording in this way that one could actually see, rather than having to guess, this nose, back, and tail of a depolarizing relaxant's action.

SUMMARY

I would like to summarize these remarks in this way. We can still think in terms of two main types of neuromuscular block. But we must take account of a number of factors conditioning their typical actions, of which perhaps the most important, because least studied, are:

(1) the ionic environment;
(2) the tissue blood flow; and
(3) the interaction together of different drugs.

Clinically, unpredictable and sometimes complex conditions must arise. But there is a real hope that simple electrophysical methods in the hands of anaesthetists might help to solve immediate problems. In addition it would throw further light on human pharmacology, to which (if one may say so) anaesthetists are making so great a contribution.

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ON CHLOROFORM AND OTHER ANÆSTHETICS

THEIR ACTION AND ADMINISTRATION

BY

JOHN SNOW, M.D.

Licentiate of the Royal College of Physicians

(*Continued from page* 390)

Case 42. A man died whilst inhaling chloroform in University College Hospital on October 11th, 1854. The patient was a shoemaker named George Sands, aged 39, and of rather bloated aspect. He inhaled chloroform whilst Mr. Erichsen was endeavouring to introduce a catheter and had the intention of puncturing the bladder if not successful. The patient was made insensible, and the chloroform was left off, but was reapplied on account of the patient making some expression of pain. "Probably about two minutes of the second inhalation had elapsed, when the man became profoundly insensible, and began to snore with a peculiar and very profound stertor. His face at this time was suffused and flushed, and the inspirations were drawn at rather prolonged intervals. Mr. Erichsen's attention was at once excited by these symptoms, and, desisting from the use of the catheter, he immediately commenced dashing the patient's face and chest with water. The chloroform had, of course, been removed. In the course of about a minute, the noise with the breathing gradually lessened, and it became apparent that the respiration was ceasing altogether. Mr. Erichsen now put his finger into the patient's pharynx, and dragged forwards the root of the tongue; at the same time attempting artificial inflation of the lungs, by applying his own mouth to that of the man. The latter plan did not appear to succeed well, and was almost immediately substituted by the more usual mode of artificial respiration, by compression of the chest, which was kept up most vigorously. The man's pulse had been felt by the administrator [Mr. Carnell] to be still beating some little time after the commencement of the alarming symptoms and the cessation of respiration. Artificial respiration had been employed for about four minutes, when the man, whose countenance had meanwhile retained its colour and an expression of yet remaining life, began to breathe again. A very short intermission of artificial assistance having been made, he drew spontaneously three or four inspirations; but, as each successive one was more feeble, the artificial aid was at once recommenced. About five minutes from the commencement the galvanic apparatus was got in readiness and applied. It produced, however, no benefit; and from this time the patient lost colour in the face and was evidently dead. . . . The form of inhaler which had been employed was the one in ordinary use at this hospital, viz. a folded piece of lint. The administrator's hands and the

patient's face had been covered during the inhalation by a towel."*

At the examination of the body seventy hours after death, extensive fatty degeneration of the heart was met with. The cavities of the heart were empty, owing no doubt, to the artificial respiration.†

The above case differs to a certain extent from those previously quoted, inasmuch as the first symptoms of danger were those of profound coma, and of threatened death by apnœa, as a consequence of the action of the chloroform on the medulla oblongata and nerves of respiration. In addition to this cause of danger, however, the chloroform present in the lungs at the moment when the inhalation was discontinued must have acted directly on the heart or the prompt assistance of so able an authority on asphyxia as Mr. Erichsen, the moment the breathing was suspended, would surely have restored the patient. The mode of death, although not exactly the same as that in Experiment 24 (Vol. 27, p. 416), differs from that in the previous experiment, where the heart's action was good and distinct after the breathing ceased; it resembles the mode of dying in many animals that I have killed with chloroform; being, in fact, a combination of death by apnœa and cardiac syncope, which generally occurs when the quantity of vapour in the respired air is intermediate between that in Experiments 23 and 24, or somewhere between 5 and 10 per cent.

A great peculiarity in the way in which chloroform was administered in the case we are considering was that the head and face of the patient were covered by a towel, under which the lint wetted with chloroform was held. The countenance and state of respiration could not be observed in this mode of giving chloroform; the person administering it had to depend almost entirely on the pulse; and except for this cause, there is every reason to conclude that the chloroform would have been withdrawn in this instance in time to save the patient. It was not apparently till a peculiar and very loud stertor attracted the attention of the operating surgeon himself, that the inhalation was discontinued, and the face was already suffused.

This plan of administering chloroform with the head and shoulders of the patient covered with a towel, was introduced by Mr. Clover, who was for several years a resident officer of the institution; and it is but right to state that it led to no accidents in his hands; in those of his successors it was, however, less successful; three accidents having occurred in a little more than a year and a half. I much regret to find that Mr. Erichsen recommends this method of giving chloroform in the edition of his work on surgery recently published.

Case 43 occurred in Guy's Hospital, on December 5th, 1854. The patient was a woman whose leg Mr. Birkett was about to amputate on account of malignant ulceration. She gave her age as fifty-six, but appeared ten years older. "In each eye was a fairly marked arcus senilis, but the woman was not known to have suffered any symptoms referable to thoracic disease. . . . The administration of the anæsthetic was conducted by Mr. Bryant,

* Med. Times and Gaz., 1854, vol. ii, p. 390.
† Ibid., p. 442.

the inhaler used consisting of a fold of lint, rather larger than an out-spread hand, and protected on its back by a piece of oiled silk to prevent wasteful evaporation. . . . In the first instance, about a drachm of the fluid was poured upon the lint. The patient inhaled it kindly; and, after about two minutes, another drachm was added. A stage of excitement now followed, during which the limbs required to be held. Insensibility was just fully established, and Mr. Birkett was on the point of commencing the operation, when Mr. Callaway, who was compressing the femoral artery, exclaimed that the pulse had suddenly ceased entirely. The wrist was examined and the same found to be the case. Almost immediately afterwards, a long-drawn inspiration, attended with a deep sighing noise, was observed. For two or three breaths the cheeks puffed out during expiration; the respiration next fluttered, and then ceased. Mr. Birkett at once put his finger into the patient's mouth, and drew forward the tongue, artificial respiration being meanwhile commenced by assistants by means of compression of the chest. A few slight inspirations were attempted by the patient subsequent to the commencement of the artificial assistance; but they did not continue, and no sign of vitality was ever afterwards shown. . . . It must be noted, that the woman had been very pale both before and throughout the exhibition, and that no change in her appearance was perceived when the alarming symptoms occurred, excepting that the superficial veins of the neck and temple became distended with blood. The cessation of the pulse was most sudden. Mr. Callaway stated that it was not preceded by the least premonitory fluttering, the stroke having been good one beat, and entirely wanting the next. This order of symptoms was of course suggestive of death beginning at the heart, (cardiac syncope), the cessation of the functions of the nervous system having been markedly subsequent to that of the circulation. . . .

"Autopsy, twenty-four hours after death (conducted by Dr. Wilks). The corpse was much emaciated, and the rigor mortis imperfect. The lungs were much congested with fluid blood, which ran out after incision of their substance. The heart was of normal size, but soft and flabby; its left side was nearly empty, the right being distended with fluid blood The left ventricle was of good thickness; its muscle of a deep colour, not encroached on by fat, or in the least mottled, the only observable departure from a healthy state being its flabbiness. The right ventricular wall was very thin, the subserous fat having in some parts almost taken the place of the muscular tissue. The layer of the latter, however, although much thinned, had still a good colour, and did not appear to the naked eye as degenerated, an observation which may apply also to the carneæ columnæ. The liver was in an early state of cirrhosis, and the kidneys were both of them mottled, and contained numerous small cysts in the external part. The brain was rather paler than usual, its convolutions appeared shrunken and atrophied, and there was a quantity of serous fluid in the arachnoid sac and in the ventricles. There was general atheromatous disease of the arterial system, both in the head and other parts of the body.

The blood was universally fluid, and of a dark colour."*

As far as could be estimated, the time occupied by inhalation was about three minutes in this case.

Case 44 occurred at the Royal Ophthalmic Hospital, on April 10th, 1855, in a man on whom Mr. Bowman was about to perform excision of the left eyeball. The patient, named John Cannon, was forty years old and was moderately stout, florid, and healthy-looking. He had generally led a temperate life. The disorganisation of the eye was the result of injury.

"The inhaler used was the one devised and recommended by Dr. Snow. . . . The administration was intrusted to Dr. Playne, of King's College Hospital. In the commencement of the inhalation, the valve of the mouthpiece was so turned as to admit an abundant supply of air, a point to which Mr. Bowman directed personal attention. During the first four minutes (more or less) nothing unusual occurred. Dr. Playne, who had his finger on the pulse, had noticed that it had rather increased in fulness, and was of good volume. Rather suddenly however, just as the anæsthetic appeared to be producing its effect, symptoms of excitement occurred. The eyes became fixed and staring, the arms outstretched and rigid, and the face contorted. It was now impracticable to feel the pulse, on account of the tossing about of the arms; but, as is usual in such conditions, the respiration was noticed to be all but, if not quite, suspended by the spasmodic fixture of the chest. The inhaler was at once removed, and the face and chest of the patient dashed with cold water. Almost immediately after, as the respirations had become extremely feeble and sighing, Mr. Bowman commenced practising artificial breathing, by the application of his own mouth to that of the patient. By this means, the chest was made to fill very completely, and the process was kept up almost without intermission for from five to eight minutes. During the first three or four minutes after the alarm began, the patient continued at times to make slight sighing efforts at voluntary inspiration, and the case was not thought by those looking on, to be by any means hopeless. At length, however, these finally ceased, and from that time it was apparent that the man was dead. . . . At the first opportunity which occurred for examining it after the spasmodic struggling had commenced, the pulse was found to be extinct, and it remained so ever after, although there were, as stated, feeble efforts at inspiration. The patient's countenance changed somewhat during the treatment, but was mostly suffused and congested."

At the examination of the body forty-eight hours after death, "the sinuses, and the veins of the brain generally were much congested, and there was some œdema of the brain substance. The heart, excepting some slight deposits on the curtains of the mitral valve, was healthy. Its muscular substance was easily lacerable. The right ventricle contained a considerable quantity of fluid blood, the left was nearly empty. There was some pleuritic adhesions, and the lungs generally were congested, being also in some parts full of air. The blood in every organ examined

* Med. Times and Gaz., 1854, vol. ii, p. 501.

was fluid, and without trace of coagulation."*

It does not seem that the inhaler used in this case was employed with the object for which it was contrived—that of regulating the amount of vapour in the inspired air; and I do not know whether the bibulous paper was arranged properly in the interior.

Case 45. On September 8th, 1855, a lady, aged twenty-nine, the wife of a physician, died suddenly whilst inhaling chloroform for the relief of facial neuralgia. I was sent for when the accident happened, and arrived twenty minutes afterwards. I found the deceased lady without any sign of life. The face and lips were very pallid. The husband was performing artificial respiration by mouth to mouth inflation of the lungs, and alternate pressure on the chest, and I assisted him in this for a long time, though with no hope that anything could be of service. Dr. Barker, of Grosvenor Street, arrived soon after me, and assisted in the same measures. An inhaler was employed in this case consisting of a face-piece, like the one above delineated in this work, and a bent metal tube lined with bibulous paper. Two quantities of ten minims each had been inhaled, with some relief to the pain, and without causing unconsciousness when the inhaler and the chloroform were put away in a closet; but the patient begged to have more chloroform, in order to be completely relieved of the pain, as she had been on a previous day. Ten minims more chloroform, as I was informed, were put into the inhaler, and the patient, being seated on the sofa, began to inhale very eagerly, but had no sooner commenced than she gave a sudden start, as if taken in some kind of fit. Her husband laid her on the floor, but she evinced no further signs of life.

There was no inspection of the body.

The only explanation which the case admits of is that, in her eagerness to get relief, the patient took one or more inspirations of air very highly charged with vapour. The symptoms were those of death by cardiac syncope.

(*To be continued*)

* Medical Times and Gazette, 1855, vol. i, p. 363.

SOCIETY NEWS

THE SOCIETY OF ANAESTHETISTS OF THE SOUTH-WESTERN REGION

A meeting of the South-Western Region was held at Oxford on Friday and Saturday, June 22 and 23, 1956. The following programme of lectures was arranged:

Friday, June 22

2.5–4.15 p.m.
Lecture and Demonstration by Professor J. H. Burn, Department of Pharmacology, University of Oxford: "The Production of Auricular Fibrillation in the Dog Heart-Lung Preparation and its arrest by Potassium Chloride."

4.45–6.0 p.m.
Lecture demonstration by Dr. H. G. Epstein, Nuffield Department of Anaesthetics: "Some Aspects of Anaesthetic Explosions."

Saturday, June 23

9.0–10.30 a.m.
Lecture Demonstration by Dr. R. Bryce-Smith, Nuffield Department of Anaesthetics: "Anaesthetic Equipment in Oxford."

10.30–11.0 a.m.
Presidential Address by Professor Sir Robert R. Macintosh.

11.30–12-45 p.m.
Lecture demonstration by Dr. A. Crampton-Smith, United Oxford Hospital: "The Indications for Lassen's Method of Treatment by Tracheotomy and Intermittent Positive Pressure Respiration."

BOOK REVIEW

The Life of Sir John Bland-Sutton. By W. R. Bett, Published by E. & S. Livingstone Ltd., Edinburgh. Pp. 100; illustrated. Price 20s.

Dr. Bett has succeeded in the very difficult task of giving us a picture of the many and varied activities of this most remarkable man.

It may be argued that a continuous account of his life from birth to death, and a record of the incidents in it as they occurred might have given a more vivid idea of the man himself as known by those who worked with him over a long period of years, but it would be difficult to marshal them all in chronological order in the case of Bland-Sutton, whose versatility was so great and interests and accomplishments so varied.

The author's task has been immense and must have involved him in a great amount of research, and the expenditure of much time tracing Bland-Sutton's early original work in the 1880s and early 1890s. He is to be congratulated on the result, and the medical profession should be grateful to him for undertaking it.

When one considers all the work Bland-Sutton did in anatomy, odontology, comparative anatomy at the zoo, and his original work in the field of gynaecological surgery, as well as contributing numerous papers to scientific journals and societies, it is difficult, particularly in these days, to realize how it could all have been accomplished without even the help of a secretary.

Even later when books from his pen began to appear and seven editions of *Tumours Innocent and Malignant* were produced at a time when his private practice was at its greatest, he still wrote everything himself in the neatest of handwriting and all correspondence was answered by return of post. As Dr. Bett points out, one is staggered by the man's " infinite capability for work ".

It is perhaps a pity so much mention has been made of Bland-Sutton's *Story of a Surgeon,* as it was written at the request of his great friend Rudyard Kipling, who should have realized that his friend's powers, at this time, were rapidly failing, and he was not capable of doing himself justice.

Dr. Bett, by dividing his book into sections dealing with his hero's various activities, has been able to bring out the value of his original creative work and to emphasize the enormous influence this work had on subsequent pyloric surgery. Bland-Sutton laid the foundation on which Victor Bourneg and others who had sat at his feet at Chelsea, were able to build the structure and technique of present-day gynaecological surgery.

Mention has been made of a certain crudity in his surgery, particularly in operations other than abdominal. This allegation is true, but the surgeons of today who make this criticism can hardly compare modern technique with that of sixty years ago. In those days speed and delicacy of touch had to achieve what today is accomplished by improved methods of anaesthesia and the availability of blood transfusion.

The writer recalls a Saturday afternoon when Bland-Sutton did two hysterectomies, one ovarian cyst, a cholecystectomy, and an appendicectomy, between 1.30 p.m. and 3.45 p.m. without any appearance of haste, and when he saw the patients next morning all were sitting up in bed reading their Sunday papers. His results were good, and he was never tired of teaching that " surgery which killed the patient was not successful "; a point which sometimes seems to be overlooked today.

Dr. Bett also so rightly points out that Bland-Sutton not only inspired those who worked with him, but commanded their admiration and deep affection.

Dr. Bett's book is of great interest not only to the medical profession but to all who are interested in medical history.

Raymond E. Apperly

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